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The Oxford Medicine

BY VARIOUS AUTHORS

EDITED BY

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CHAPTER I

DISEASES OF THE BRONCHI

By C. F. HOOVER

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ORIGIN OF TRACHEO-BRONCHIAL INFLAMMATIONS

Tracheo-bronchial inflammations originate from metastatic infections, from inhalation of infectious agents and mechanical or chemical irritants, and from chilling of the body surface.

Metastatic Infections

Metastatic infections of the bronchial path offer the basic problems of susceptibility and immunity common to infections elsewhere in the body.

Inhalation

When we consider the violent inflammatory processes which attend inhalation of some irritating chemical substances, and the accessibility of the entire air passage to infectious agents and inorganic substances, we marvel at the severity of the inflammation which is caused in some instances and the immunity which apparently exists toward other invading substances that are carried into the remotest air passages by the ventilating air.

Why pneumokoniosis is not a much more common affection than we find it to be, is unexplained, and why bacterial inhabitants of the mouth and pharynx, which have a saprophytic existence in these locations, become virulent pathogenic organisms in the lower air passages, also is in want of a satisfactory explanation. The normal respiratory membrane enjoys a certain protective function against invading organisms, but just what happens when this immunity is lost is one of the unsolved problems.

The defense of the upper air passages against infections has been amply demonstrated in bacteriological studies of the nasal and pharyngeal mucus after bacteria had been sown upon the mucous membrane. All the bacteriological studies show that the mucous secretion offers a formidable defense against the local invasion of bacteria. The course of the inspired air through the nasal passages, the angulation at the pharynx, the stenosis at the glottis, and then again the sharp angulation at the bifurcation of the trachea and the branching of the bronchi, give excellent opportunity for the mucosa to capture organisms and foreign materials which are carried in with the inspired air.

The defensive element in the anatomical structure, just referred to, consists in the friction of the inhaled air against the mucous surface which results from deflection of air currents by intercepting surfaces, as in the nose and larynx, and by change of direction, as in the nasopharynx and at the bifurcation of the trachea and further branching of the bronchi. In spite of this protection, which experimental infection shows is more effective than one might a priori expect, we have not in the mechanical protection of the mucous lining of the air passages an infallible guard against invasion of the remote air passages by a great variety of organic and inorganic material suspended in the respired air. The total area of the mucosa of the tracheo-bronchial path leading up to the respiratory units is very small compared with the total area of the true respiratory membrane, but so far as defense against invasion is concerned, investigation shows this function to be confined to the bronchial path. It is along the bronchi that lymphatics and phagocytes abound. There are no lymphatics about the air cells and the alveolar epithelia do not possess any phagocytic property. In medical practice we see a differentiation and association between bronchitis and air cell infection which is analogous to the relation between lymphangitis of an extremity and infection of the blood stream. Bronchitis is the most common disease of the air passages. The arrangement of the lymph vessels and the defense of the bronchial mucosa account for the more frequent occurrence of disease of the bronchi when we consider air-borne invading agents. But when internal disturbances are considered, we find no adequate explanation for the varying and differentiating vulnerability that exists in the air cells and in the bronchial tract.

Chilling of Body Surface

Chilling the surface of the body is attended by prompt hyperemia of the Schneiderian membrane. Whether this hyperemia is a response to purely nervous agents or is a result from activation of some substance by chilling of the blood exposed to the cold, is not clearly understood. We do know, however, that lowering the temperature of the blood by exposure to cold will increase susceptibility to blood infections, but this does not seem applicable to bronchitis which is the result of exposure to cold.

In the case of susceptibility to blood infections, we are dealing with a lowered temperature of the entire mass of circulating blood. In the case of bronchitis from cold, we are dealing with a response to chilling of a small portion of the blood. In paroxysmal hemoglobinuria a frigore we are dealing with the activation of a hemolytic agent contained in the blood. It is possible that a small portion of the total circulating blood may be chilled and as a consequence give rise to some activating agent which will cause hyperemia and edema of the tracheo-bronchial mucosa. The problem which remains to be solved is whether this local response to chilling of a portion of the body's blood is due purely to activation of some chemical substance in the chilled portion of the blood, or whether there may be, in addition to this activated substance, an exaltation of the virulence of bacteria which are constantly invading the tracheo-bronchial mucosa. The bacteriology of the tracheo-bronchial path is extremely difficult to interpret. It is difficult to know with certainty what organisms have merely a saprophytic part and what ones play an etiological role in bronchial disease. The significance of the presence of bacteria in the air passages is much in doubt, with the exception of a very few bacteria, such as the tubercle bacillus, the spirochaeta pallida, and possibly the spirochete which has been described and interpreted by Castellani in a certain form of hemorrhagic bronchitis. When we are dealing with organisms which are normally found in the buccal and nasal cavity, we are quite at a loss to interpret their exact role in the causation of bronchitis. Whether their exaltation is due to the presence of a chemical substance in the blood or to symbiosis with some other organism, is an unanswered question.

SENSATION OF BRONCHI

The upper tracheo-bronchial mucous membrane is exquisitely sensitive, but we know the smaller bronchi and bronchioles are not sensitive to the presence of foreign substances, and we have ample proof of this in the frequent occurrence of disease of the pulmonary parenchyma and remote bronchi without cough. Just where the line of demarcation may be between sensitive and anesthetic mucosa is not known, nor do we know whether there is a sharp line of demarcation between the sensitive and asensitive parts, or if there is a gradual diminution in sensitiveness as we progress from the larger to the smaller bronchi. We do know, however, that foreign bodies may lodge beyond the second division of the bronchi and cause no sensory experience on the part of the patient until secondary inflammatory processes will have extended the area of inflammation to large sensitive bronchi. In the trachea and large bronchi there is an exquisitely sensitive nerve supply. As we proceed toward the smaller ramifications of the bronchi, the mucosa does not change in its essential anatomical structure, but the walls of the bronchi with diminishing lumina do change in a manner which strongly suggests the progressive difference in structure between the aorta and its branches. In the smaller air tubes, muscular tissue constitutes a much larger proportion of the wall; the elastic fibrous tissue and cartilaginous tissue gradually disappear, until, in the bronchiole before its entrance into the antrum, we have a structure which is strikingly like that of the arterioles. The submucosa in the trachea and large and small bronchi admits of very marked accumulations of lymph. An irritative lesion in the trachea and large bronchi may cause complete occlusion of the lumen, as was frequently seen during the epidemic of influenza during the winter of 1918-1919. Occlusion of a large bronchus from edema of the mucosa was seen in a number of instances in children. Occlusion of the trachea from edema is a rare occurrence, but was probably seen many times during the great epidemic of influenza.

The character of the tracheal mucosa and that of the mucosa in the bronchi and bronchioles are the same. However, edema in the large and small air tubes will have very different functional results. The same degree of edema in a large and small air tube may mean complete occlusion of the small tube, whereas in the large tube there will not be sufficient encroachment on the lumen to cause any functional disturbance. Fortunately, inflammatory edema of the tracheo-bronchial mucosa is rarely sufficient to cause occlusion in the trachea, but it is frequently sufficient to cause occlusion of some of the large divisions of the bronchi.

Thus far I have observed the exquisite sensory nerve supply to the large passages and the want of any sensory supply to the small air passages. However, as the sensory response diminishes in the progress distally in the air passages, the neuro-muscular activity increases. There is sufficient muscular fiber in the bronchi to cause visible changes in the lumen, but neuro-muscular action is greatly exalted in the bronchioles;

so as we progress distally in the air passages, the sensory supply which lies within the field of consciousness disappears, but in the distal portions, as the sensory supply fades, we find an exquisite lability in neuromuscular equlibrium, when we consider the relative sensitiveness of the sympathetic nerve supply in several fields of unstriated muscular fiber.

The nerve supply to the arterioles of the skin is exquisitely sensitive, as is shown by the sensitive response of the arterioles of the skin to adrenalin as compared with the response of the arterioles of the mesentery. An extremely small amount of adrenalin in the blood, such as results from a subcutaneous injection of 20 minims (1.3 c.c.) of a 1:1,000 solution, is sufficient to allay the edema of urticaria, whereas the same amount does not have an appreciable effect on the total blood pressure. This means of course that there is much more labile neuro-muscular balance in the arterioles of the skin than in the splanchnic distribution; otherwise, if there were the same blanching and blushing in the splanchnic supply that we have in the skin, there would be frequent modifications of consciousness.

It is interesting to observe that the same amount of adrenalin which is required to influence the arterial supply of the skin is sufficient to modify muscular tone in the bronchial distribution. The minimum dose of adrenalin which will stimulate the arterioles of the skin is sufficient to inhibit the tone of unstriated muscular tissue of the bronchioles.

Relation Between Pathological Processes in Bronchi and in Lungs and Pleura

Pathologically, it is rare to find a disease of the tracheo-bronchial path without secondary and consequent pathological changes in the air cells of the lung. Disease of the bronchial path readily extends by contiguity to the air cells and into the pleura, but we may have inflammation of the pleura attending bronchitis without intermediate changes in the air cells. The anatomical relations between the arterial and venous supply to the bronchial tract and the pleura from the bronchial artery and bronchial veins, and the anatomical relation between the subpleural lymph spaces and the peribronchial lymph spaces, are such that we may have an extension from infection in the bronchial path to the pleura without any involvement of the air cells. So there is probably a good anatomical basis for the chest pains which frequently attend bronchitis when there is no intervening pneumonia.

Petzetakis[1] from a military hospital at Athens made the observations that pleurisy is a very frequent accompaniment of mild bronchial infections in the absence of any demonstrable pneumonia. In fifty-one cases of bronchitis he succeeded in demonstrating the presence of fluid in the pleural cavity in thirty-eight. This mild degree of pleurisy did not influence the course of the disease. The fluid was sometimes unilateral but often bilateral. The fluid was sero-fibrinous, rich in cells and sterile. The quantity recovered varied from a few c.c. to as much as 50 c.c. The puncture was made in the ninth and tenth interspaces in the postero-axillary line. The physical signs were very few, and showed only a slight diminution in resonance with little impairment of mobility of the base of the lung.

Pathological Physiology of Bronchitis

Besides the evidences from pathological anatomy which attend bronchitis, we have disturbances in the physiology of respiration which are very striking and may at first sight seem to be disproportionate to the degree of pulmonary movement. There are several functional disturbances which must be considered in bronchitis:

Unrespired Blood

Should edema within a large branch of a bronchus shut off the ventilation of a portion of the lung, we shall have from the lung area supplied by the affected bronchus, unrespired blood delivered to the left auricle by the pulmonary veins which come from the involved area. The contribution of unrespired blood to the aortic stream means that a patient will have anoxemia with an increased partial pressure of carbon dioxide in the blood of the left side of the heart. The patient can readily compensate for the increase in partial pressure of carbon dioxide by increasing the ventilation of the free portions of the lung, but he cannot compensate for the anoxemia. For instance, the patient may have an occlusion of a large bronchus which will produce cyanosis without conscious air hunger, although the patient will be superventilating the free portions of the lung. We must not employ superventilation and air hunger as identical terms. Air hunger is a subjective experience and not an objective sign. In moderate exercise, ventilation of the lung may be increased two or three times that which is employed while at rest, but the subject will be unconscious of any respiratory discomfort. And so a patient lying at rest in bed may superventilate the free portions of his lung and compensate for the increased carbon dioxide from unrespired blood contributed to his aortic stream, and not complain of respiratory discomfort, but at the same time there will be a sufficient contribution of anoxemic blood to give him a distinct cyanotic color.

This can be confirmed in a very simple experiment on the dog. A preliminary tracheotomy is performed and a pledget of lamb's wool is pushed down into the right bronchus. There is no evidence of great respiratory distress, but if blood is withdrawn from the femoral artery while the tampon is in the right bronchus, the blood will be found to have taken on a decided venous color; and when the plug is withdrawn from the bronchus, the arterial blood will immediately regain its original arterial color.

Another source for the admixture of unrespired blood with the aortic stream lies in the presence of moisture within the bronchial path, and the amount of moisture need not be very great to accomplish this. Moisture within the bronchial path may be due directly to the inflammation of the mucosa, and it may be the result of "dry-cupping" the lung. Suppose the obstruction to the entrance of air is in the trachea, so that the patient must greatly increase the minus pressure on the distal side of the stenosis to gain an adequate minute volume of ventilated air. This means, of course, that the minus pressure on the distal side of the stenosis will be very greatly increased, and it will have the same effect on the bronchial mucosa and respiratory membrane that "dry-cupping" will have on the skin—that is, provided stenosis is severe and lasts a sufficiently long time. This I conceive as one of the sources for the complication of moisture within the air spaces which invariably attends prolonged stenosis of the trachea or a large bronchus. The moisture is not due entirely to extension of the inflammatory processes or infection, but is really what may be legitimately termed an aspiration edema. Now, whether the moisture within the bronchial path is of inflammatory origin or is due to the changes described, the effect on pulmonary ventilation will be the same. During respiration all the mobile serum within the bronchial path will be churned into foam and will greatly impair the ventilation in certain regions of the lung. This impairment of ventilation will result in an anoxemia, which may frequently be very pronounced without any accompanying air hunger. If the cyanosis is due to moisture within the bronchial path, and the consequent alveolar air foam is changed into oxygen foam by giving the patient pure oxygen to breathe, then we can compensate for the anoxemia, and the patient's cyanosis will disappear. This will happen whether or not the patient has air hunger; and should the moisture be in sufficient quantity to produce anoxemia with air hunger, the anoxemia will disappear. The patient's blue color will give place to a normal pink, but the experience of air hunger will not be modified. So in cases of bronchitis associated with cyanosis and air hunger, and in patients with severe bronchitis in which cyanosis and air hunger both exist, the patient cannot tell from his subjective experience when he is breathing pure oxygen and when he is breathing atmospheric air. This dissociation between cyanosis and air hunger attending moisture within the bronchial tree and its method of diagnosis are mentioned because it is frequently very important in the management of bronchitis associated with cyanosis to determine definitely whether moisture or some other complicating factor is responsible for cyanosis. It is obvious that, if a patient is cyanotic on account of moisture within the air passages of the lung, the best therapeutic measure will be to live in a climate which has a low relative humidity. If the inhalation of pure oxygen for a period of five minutes will not cause the cyanosis to disappear, we must assume some other factor than foam is responsible for the cyanosis, and we cannot reasonably expect that life in an area of low relative humidity will cure the patient's anoxemia.

The Velocity of Ventilating Air

A normal subject at rest will evolve 20 c.c. of carbon dioxide in each respiratory cycle. The fall in partial pressure of carbon dioxide from the effluent blood of the pulmonary circulation is equal to only about 12 mm. Hg.; the ventilating volume of air with each respiration will be only about 400 c.c., and the time occupied in this evolution of carbon dioxide will be a few seconds. We know that the lung is the most exquisite tonometer or instrument to balance the partial pressure of gases in solution in the blood with the partial pressure of gas in the surrounding air of which we can conceive, and the perfection of this tonometer is due to the extremely thin layer of blood which is in contact with the respiratory membrane on its internal side. This layer of blood has only the thickness of a red corpuscle. The membrane itself is only about 1/1,000th of a mm. in thickness, and the total area of the respiratory membrane is about 100 square meters.

Now in addition to all these factors which are essential to maintain the tonometric function of the lung, there seems good reason to believe that the manner in which the ventilating current of air arrives and leaves the respiratory unit is also essential. The velocity of air current over a bed of carbon-dioxide-containing substance is a determining factor in the amount of carbon dioxide the ventilating air will take up from the bed. I am assured from a very dependable chemical engineering source that where this chemical problem has entered into industry, the velocity of the current of air is a determining factor as well as the volume of ventilation and the area of the bed. Now, this problem of velocity of ventilation and its significance in diseases of the air passages has not been worked out physiologically, but it seems very likely that the slowing of the velocity of a ventilating air current within the respiratory units of the lung may be a factor in both cyanosis and air hunger.

Volume of Lung in Stenosis of the Upper Air Passages

The following clinical experience suggested the experiment which was employed on animals. A girl, ten years of age, with laryngeal diphtheria, had symptoms which simulated bronchitis with asthma. There was marked inspiratory and expiratory dyspnea, and the volume of both lungs was sufficiently increased so that the costal borders were drawn toward the median line during inspiration, as seen in bronchiolar spasm. The question arose whether stenosis in the trachea would give the same increased pulmonary volume as attends hypertonus of the bronchioles. Into the trachea of a dog was inserted a cannula which connected with a Y-tube, and, at the end of an automatic inspiratory phase, the arm of the tube which communicated with the atmosphere was closed and the other arm of the Y-tube opened, which communicated with a three-liter bottle, which was under a minus pressure measured by a mercury manometer. At the height of the inspiratory phase, when the tube communicating with the air was closed and the tube communicating with the minus pressure in the bottle was opened, the thorax of the dog was compressed and the barometric pressure in the bottle measured after the maximum amount of air was displaced from the lung by compression. It was found that when the animal was breathing against an artificial stenosis in the cannula, a larger amount of air would be recovered from the lung by this method than when the dog was breathing through the unobstructed cannula.

It seems that a stenosis in the trachea will cause an increased volume in the lung, but it does not cause the same degree of emphysema as occurs with bronchiolar hypertonus. When stenosis is employed in a cannula inserted in the trachea of a dog, the costal borders move away from the median line during inspiration, although the stenosis may be sufficiently severe to cause a very marked anoxemia. Even when blood drawn from the femoral artery contained only half the normal amount of oxygen, the costal borders widened during inspiration.

During the influenza epidemic of 1918, a young girl, well grown and of strong physique, was seen at the end of the second day of her illness. There was violent tracheo-bronchitis from the beginning of her infection, but at the end of the second day there was severe stenosis of the trachea due to inflammatory edema of the mucosa, which could be seen by the aid of the laryngoscope, well below the vocal cords. There were no evidences of pneumonia, and no evidences of capillary bronchitis. The patient was doing her utmost to overcome the obstruction to inspiration and expiration. In fact the stenosis was so severe that the patient died from this cause within six hours, but the costal margins diverged during inspiration during all this violent struggle against tracheal stenosis. It seems that although stenosis in the trachea will cause a moderate emphysema, it will not give rise to the severe emphysema which accompanies stenosis of the bronchioles, whether it is caused by muscular hypertonus or swelling of the mucosa.

The mechanism of expiration against stenosis in the trachea differs essentially from the mechanism of expiration against bronchiolar obstruction, but just where the difference lies is not clearly explicable with our present knowledge of the mechanism of pulmonary ventilation. It is rare that one can have the opportunity of seeing a pure stenosis of the trachea or large bronchi unaccompanied by bronchitis or bronchopneumonia beyond the point of obstruction. The secondary pulmonary involvement will greatly complicate symptoms which attend a pure tracheal stenosis.

Stenosis of the Bronchi

Uncomplicated stenosis of a large air passage in the lung is a rare occurrence. Both intrabronchial and extrabronchial causes of stenosis are attended with so many complicating factors that we rarely are privileged to see the pure clinical symptoms.

Quite apart from the symptoms incidental to growths of the mediastinum, and also quite apart from the nature of an obstructing substance in the bronchus and consequent bronchitis and bronchopneumonia, there are symptoms which are ascribable purely to obstruction of the bronchus. A number of observers have commented on the paucity of symptoms in obstruction of a bronchus. One writer in fact says he could see very little impairment of excursion on the affected side. The impairment of thoracic excursion is much less conspicuous when the bronchus leading to a portion of lung is obstructed than when the same area of lung is consolidated from disease or when the visceral pleura is thickened by obsolete pleurisy. If a bronchus is completely obstructed, the contained air will be absorbed by the circulating blood, and this absorption will be attended with atelectasis. But before the atelectasis occurs in acute obstruction and when the obstruction is severe in chronic cases, the affected portion of the lung will still be capable of some excursion when the minus pressure in the pleural cavity is lowered during inspiration. The contained air is very elastic and is capable of expansion during inspiratory effort, which will be sufficient to permit some excursion of the overlying ribs. On account of this fact, the degree of costal excursion may lead one to overestimate the amount of ventilation which is actually taking place in the underlying lung. There may be sufficient obstruction in a bronchus to greatly impair the ventilation of one lung, so that the minute volume of air passing into the affected side will be very much less than the minute volume of ventilating air on the unaffected side, and yet the stenosis will admit of the free passage of sound and of fremitus due to vocalization. There may be sufficient encroachment upon a bronchus of one lung to cause a demonstrable diminution in the size of the lung and to impair the excursion of the entire lung, and still the respiratory sound and tactile fremitus may be little affected. In just such a case there may be no evidence of bronchitis on the affected side. Suppose the lumen of the left bronchus be compressed to one-half the original size, and assume that the patient will have a respiratory excursion which will amount to 700 c.c. of tidal air; 500 c.c. of this tidal air may go into the right lung, and only 200 c.c. into the left lung. Such a condition would not cause the patient any discomfort when he is at rest, but of course would diminish his cardio-respiratory function so that active exercise would be forbidden. The patient would not have air hunger when at rest. There would be diminution in the respiratory excursion of the affected side; and inasmuch as with the required inspiratory effort there is free entrance and exit of air into the unaffected side, there is superventilation of the clear side to compensate for the diminished tidal air passing the affected bronchus. This can be accomplished by very moderate increase of the minus barometric pressure within the pleural cavity; and inasmuch as unilateral stenosis under these conditions does not result in a great increase of the velocity of tidal air, there may be no unusual respiratory sound heard over the affected side, whereas if the same degree of stenosis occurred in the trachea or simultaneously in both bronchi, the requisite ventilation would demand a great increase in the velocity of air at the point of stenosis, and this increase in velocity, with consequent eddies beyond the point of stenosis would produce loud râles, which would be audible throughout the affected bronchial tree.

Recently such a case came under my observation. The patient had an aneurysm of the transverse and descending arch of the aorta. There was a strong tracheal tug. The total volume of the left lung was demonstrably diminished in all its diameters. The excursion, although moderate in all dimensions, was very much less than on the right side. With the exception of the apex of the left lung, which was partially compressed by the aneurysm, there was no dullness over the remaining portion of the lungs. The tactile fremitus was well preserved; the spoken voice was well conducted, and there were no adventitious sounds audible anywhere over the lung. The patient had a good volume to all his arterial pulses; his maximum systolic pressure was 150, and his minimum diastolic 90. There was not the slightest evidence of any stasis in the systemic veins or in the pulmonary circulation. The patient had no cough, and gave no evidence of bronchitis or asthma. He had been ill for several years, and had a pronounced cyanosis of his finger tips and toes, and moderately perceptible cyanosis about his lips, ears and nose. There was clubbing of the finger tips with characteristic elevation of the root of the nail. This patient had anoxemia, which had evidently existed for some months, but no air hunger when he was at rest He gave a history of very marked limitation in his ability to exercise but when he was at rest, his cardio-respiratory function was competent to maintain him in comfort. Patients with chronic cardiac disease who suffer from myocardial incompetence do not acquire Hippocratic finger tips in association with air hunger which is due to diminished minute volume of the circulating blood. It is only when some other factor is introduced which causes dissociation between anoxemia and air hunger, that the characteristic drum-stick finger ends are developed. This patient had no demonstrable impairment of his minute volume of circulating blood. There was no bronchitis on the affected side, and no pulmonary infiltration. The only manner in which his anoxemia and club fingers could be explained was on the basis of a lowered minute volume of air going to the left lung. With his right lung he was able to compensate for the increased carbon dioxide which was contributed to his aortic circulation by the pulmonary veins of the left lung, but he could not compensate for the anoxemia which was contributed to the aortic stream by the same veins.

Otto Jacobson[2] found the most striking sign of stenosis of a bronchus to be an inspiratory movement of the heart toward the affected side. By means of the orthodiascope, he demonstrated that the movement was more than 2 cm. toward the affected side, and during expiration the heart moved away from the affected side. How much movement of the mediastinum will occur toward the affected side will depend on the minus pressure which is created in the affected side during inspiratory effort. If, during inspiratory effort, the equilibrium of pleural pressure between the two sides is not maintained and there is no fixation of the mediastinum by disease, then the heart may be seen to move toward the affected side during inspiration. The diminution in excursion of the affected side is much less conspicuous than one expects to see. The disproportion between the excursion of the ribs which overlie the affected lung and the lessened pulmonary ventilation can be accounted for by the rarefication of the intrapulmonic air beyond the stenosis. This will admit of some excursion of the ribs, and an examiner may easily underestimate the significance of the comparatively slight impairment of costal excursion.

Congenital Malformation of Bronchi

Congenital malformation in the bronchi is a very rare occurrence. The severe cases are so striking that they could not possibly escape detection at an autopsy, and certainly they give very severe signs should the patient survive intrauterine life for any great length of time. In spite of the rarity of the condition, the number of cases reported in literature is rather large. The earliest case reported is one referred to in an article by Herman Meyer[3]. The description of the case is found in the works of Malpighi, in the second volume of his Leyden edition, page 349, 1687. J. Peiser[4] gives a review of cases according to age, and has collected twenty-five. Half of his cases were over eighteen years of age. The rest were in very early childhood or fetal cases.

Congenital malformation of the bronchi is very commonly found in conjunction with other deformities. An important deformity often associated with deformity of the bronchi is hernia of the lung due to defective intercostal muscles, and finding hernia of the lung might well suggest the possibility of an accompanying malformation of the bronchi. The common deformity of the bronchi arises from a failure of the bronchi to give off their vesicular buds, and the bronchi themselves seem much elongated and dilated. The lining of the bronchi retains the cuboidal epithelium with cilia, so that histologically it may in many portions look like the lining of a normal bronchus. The elongation and dilatation of the bronchi may be such as to produce a large mass of coiled tubes, which on cross-section suggest the honeycomb lung which has been described in German medical literature as a *Wabenlungen*. In other instances, besides the accumulated coils of large bronchi, there may be cystic formation. In the case described by H. L. Koeckert[5], the cyst displaced all the other structures in the thorax. The deformed bronchi may communicate freely with a normal bronchus or the communication may be nearly sealed off by narrowing of the lumen. The lumen of the enlarged bronchi may be constricted at one or more points in its length, and in some instances there is merely an elongation between the points of stenosis or between stenosis and the terminal portions of the bronchus. The deformity may present the appearance of a cyst or of the honeycomb lung, and also suggest the congenital cystic degeneration which is found in the kidney and liver. In the fetal cases the contents of the cyst and bronchi have been found to consist of amniotic fluid. Whether the subject will survive any length of time will depend entirely on the extent of the malformation and the association with other deformities of the cardiovascular system which sometimes attend the bronchial deformity. When the extent of the deformity is consistent with continuation of extrauterine life, the patients will develop a clinical picture of bronchitis with bronchiectasis, which varies with the area involved. Although there is a failure in development of the pulmonary air vesicles from the bronchi, the blood vessels of the lung, as shown by histological section, seem to be preserved, so that the pulmonary circulation through the affected part apparently remains normal in amount. At any rate, the histological appearances show no evidences of any encroachment upon the pulmonary circulation.

Meyer in his article seems to have been particularly interested in the cyanosis which accompanies this affection, and in fact had a clear idea of unrespired blood being contributed to the aortic stream from the misformed lung on account of the apparent integrity of the pulmonary vessels.

In a few instances no symptoms developed until adult life. In one case described by Marcel Garnier[6], the patient was a woman, thirty-eight years of age, on whom caesarean section was performed. Death followed from suffocative symptoms, which are not at all clearly expounded. The autopsy revealed the apex of the right lung to be honeycombed with dilated bronchi. In this case the attending physician had no knowledge of any symptoms or history of a bronchial disease.

Neisser[7] studied two cases, father and son, forty years and nine years respectively. Both patients had an atrophic left lung. Both showed dullness on the affected side, which began at the fourth rib in the axillary line and at the angle of the scapula posteriorly. The two cases of Neisser were not proved by autopsy, but the father had had bronchial symptoms from early childhood and the child had had the same symptoms, and the X-ray picture in both cases seems to have confirmed the author's interpretation.

All writers on the subject seem to agree that the lesion is not accompanied by any deformity of the chest wall, such as we find in acquired bronchiectasis with interstitial pneumonitis. The mediastinum, however, of the surviving patients is displaced toward the affected side, and the sound lung is distinctly enlarged. In some of the fetal cases, the cystic enlargement of the affected lung may attain such size as to displace the mediastinum toward the sound lung. A lobe of the lung may be involved, and although there are a few instances where only part of the bronchial supply to one lobe has been involved, as a rule the lesion involves the bronchi of an entire lobe. The surviving patients give a history of chronic bronchitis, which develops in early childhood or babyhood and continues without interims of relief. In some instances the infectious bronchitis may start in the deformed bronchi and extend into other portions of the bronchial tree, the patient presenting a picture of diffuse bronchitis with localized density of lung including dilatation of the bronchi. The ante-mortem diagnosis is attended with much uncertainty, but the condition should be reckoned with to explain cases of bronchitis with bronchiectasis which have persisted from early childhood.

Effects of Excoriatics on the Trachea and Bronchi

Prior to the Great War the effect from inhalation of excoriatic gases was well understood, but occurred with comparative infrequency. Most of the cases were due to the accidental breaking of carboys containing nitric, hydrochloric or sulphuric acid, which came in contact with wood either because the accident occurred on a wooden floor or because shavings and sawdust were strewn over the spilled acid in the process of cleaning the floor. Some instances are reported in brass founders who have accidentally inhaled the fumes from nitromuriatic acid poured into the mould preparatory to receiving moulten metal. Since the employment of phosgene and dichlorethylsulphide, the clinical symptoms and pathology have been abundantly expounded.

The primary effects of the excoriatic are apparent in the mucosa of the larynx, trachea, and the large and small bronchi. The air cells of the lung in patients, who die rapidly from moisture in the air passages, show no histological evidences of the excoriatic beyond the filling of the air cells with coagulated plasma.

Pathological Physiology of Tracheal and Bronchial Excoriation

Of course there was every degree of gas poisoning seen in military hospitals, from moderate tracheo-bronchitis without demonstrable moisture in the bronchial tree, to the very severe cases in which the patient's trachea was filled with foam. The striking thing about the appearance of these patients during the acute stage is the severe anoxemia with disproportionately slight air hunger. There is a dissociation between the carbon dioxide acidosis and the want of oxygen. Many of these patients exhibited comparatively little air hunger in the presence of severe anoxemia. In fact, many patients died, so far as could be determined, from anoxemia. Although the air hunger was pronounced, it was not sufficient to be very distressing. This dissociation between air hunger and cyanosis was due to the presence of moisture in the air passages; and whether it was due to moisture in the form of foam or to a film of moisture, which intervened between the ventilating air and the respiratory membrane, is not perfectly clear. There are some reasons, however, for believing that the foam was the determining factor rather than the presence of a layer of moisture. Carbon dioxide is twenty-five times as soluble as oxygen, and for this reason it is believed by some that the carbon dioxide is evolved from the lung more readily than oxygen can be absorbed.

If these patients were given pure oxygen to breathe, and the oxygen was given by a mask, so that the patient could not breathe atmospheric air, the symptom of cyanosis was replaced by a normal pink color, not immediately after the inhalation of oxygen was begun but after the inhalation of pure oxygen was continued for about three minutes, and although the patient's cyanosis quite disappeared, the men could not tell when they were breathing pure oxygen and when they were breathing atmospheric air. So it seemed that by this means oxygen could be supplied to the circulating blood in adequate amounts to saturate the hemoglobin, but it did not affect the evolution of carbon dioxide from the circulating plasma.

In cases of bronchitis with abundance of moisture in the bronchial tree, and in cases of cardiac stasis accompanied by foaming pulmonary edema, I have had exactly the same experiences as with the gas-poisoning cases. In other words, where moisture within the air spaces exhibits foam, inhalation of pure oxygen will dispose of the anoxemia.

During the epidemic of influenza of 1918-1919, patients who were cyanotic from edema of the lungs when the moisture did not foam, received no relief from anoxemia by breathing pure oxygen. An interpretation which seems most reasonable is that, when the patient breathes pure oxygen for a sufficient length of time to convert the alveolar air foam into oxygen foam, the area for the absorption of oxygen will be very greatly increased, whereas if the moisture fills the bases of both lungs and it is not churned into foam, then the inhalation of oxygen does not affect the patient's cyanosis.

Bronchiolar Spasm Following Excoriation

The majority of patients do not have bronchiolar spasm during the acute period of gas poisoning, but it occurs with such frequency as to deserve consideration in the treatment of any case. If the patient should have a bronchiolar spasm, the costal margins will be seen to move toward the median line during inspiration. The patients may have moderate emphysema and the borders of the lung fill the pleural sinuses, so that percussion may reveal the borders to occupy a low position, but emphysema of the lower borders of the lung will not modify the direction in which the costal margins move during inspiration. It is only when bronchiolar spasm supervenes that the costal margins move toward the median line during inspiration. If 20 minims (1.3 c.c.) of 1:1,000 adrenalin is injected subcutaneously, the bronchiolar spasm will cease in about two minutes, and the costal margins will move away from the median line during inspiration.

The Heart in Excoriation of Trachea and Bronchi

During the acute period, dilatation of the right ventricle and right auricle is not an uncommon event, but the left ventricle and left auricle do not dilate. Owing to the accompanying emphysema, it may sometimes be very difficult to percuss the borders of the dilated right auricle to the right of the sternum. But if the movements of the costal borders are observed, then the right costal borders from the subcostal angle to the eighth costal cartilage will be seen to move toward the median line during inspiration, and below and external to this point the border will move in an outward direction during inspiration. The left costal border in its entirety, under such conditions, will move away from the median line. When the effect of digitalis is procured by injecting 1/25 grain (2.5 milligrams) of digitalin hypodermically, the upper and inner portion of the right costal margin will again resume its outward movement during the inspiratory phase.

After the third day the foam in the air passages will have disappeared, and the subsequent involvement of the air passages will be due to the consequent bronchopneumonia and obliterating bronchitis and bronchiolitis, and in many instances the patients continue to suffer from a diffuse bronchitis but do not exhibit any symptoms that differ from the tracheo-bronchitis from other causes. When death came to many of these men, however, they had survived all the cardio-respiratory dangers and succumbed from hemorrhage into the white matter of the brain and spinal cord.

The Treatment of Effects of Excoriation of Trachea and Bronchi

When anoxemia is severe enough to be a menace to life, inhalation of a high concentration of oxygen by the use of a mask should be employed. The patients do not like the mask, because it gives them no relief from the air hunger which accompanies anoxemia, but the patient may be bridged over a brief period in which life is threatened by the want of oxygen. Bronchiolar spasm during the acute period responds to the use of adrenalin just as promptly as we see it in acute bronchiolar spasm accompanying bronchitis from other sources. The right border of the heart should be carefully percussed, and if the accompanying emphysema does not admit of satisfactory percussion, the movement of the right costal border will reveal the dilatation of the right ventricle and right auricle. Either strophanthin or digitalis used subcutaneously gives excellent results. One milligram (1/60 grain) of strophanthin or 2.5 milligrams (1/25 grain) of digitalin will dispose of the acute dilatation. It is perfectly useless to give oxygen in low concentrations. If the oxygen does not dispose of the cyanosis, then it is being given in insufficient quantity. During the acute stage, when the patient is menaced with anoxemia, it is not advisable to employ morphin or any drug which will raise the respiratory threshold. In the latter periods, when the patient is suffering from irritative lesions of the upper air passages, the use of morphin, heroin or codein is permissible, and in addition the inhalation of spray or steam containing benzoin, menthol and camphor, gives considerable relief from the irritation.

MUCOMEMBRANOUS BRONCHITIS

Mucomembranous bronchitis is accompanied by varying symptoms, which are determined by the disease it accompanies and by the manner in which the mucomembranous casts of the bronchi are disposed in the bronchi. Whatever the complicating pathology may be, the patients are afflicted with violent cough, which lasts a varying length of time, depending entirely on where the emerging cast may be located and how it may emerge from its bronchial bed. The patient may have severe air hunger and cyanosis, which will last from a few hours to as long as eight days, and finally, after prolonged effort at coughing, a good-sized ball of muco-purulent material is expectorated, which, when unrolled in water, reveals in many instances a very complete cast of a bronchus, with dichotymous and dendritic branches, and in fact, in some instances, the cast seems to extend even beyond the bronchioles into the respiratory unit. This curious phenomenon has been observed in association with pneumonia, typhoid fever, scarlatina, measles, Basedow's disease, pulmonary tuberculosis, disease of the mitral valve, and after paracentesis for pleurisy with effusion. The substance of these casts contains a basic material with admixtures of foreign substances and red and white blood cells, and also bacteria which are taken with the ventilating air. The study of the casts seems to indicate that the excretion is poured out in a large branch of a bronchus and its ramifications. The bulk of the cast consists of coagulated mucin. When sections are stained, they are found to respond to staining with thionin, and do not take the stain of Weigert, which is employed to identify fibrin. The cast consists of a secretory product from the bronchial mucosa. The lamellation of the casts indicates that it is a concretion which is concentrically formed. Occasionally the casts are hollow and at other times solid; so that there is very good evidence that the solid cast is simply the result of a concentrical accumulation of coagulated secretion from the mucosa of the affected tube. There is no pathological evidence to show that these casts are associated with any desquamation of the mucosa, or in fact with any severe inflammatory process of the mucous membrane.

Bacteriological study of the casts has thrown no light on the subject. The symptoms, as above described, are merely those which may attend the presence of any foreign body lodged within a sensitive area of the tracheo-bronchial path. So the manner in which the cast disposes of itself within the bronchial tree will determine how much cough, air hunger, cyanosis, and attending moisture in the bronchial tree may develop.

Several observers have seen patients who had mucomembranous bronchitis, as well as membranous colitis and mucomembranous dysmenorrhea. Roger[8] studied the question of coagulation of mucin, and his observations started from the fact that the coagulated mucin was found in the lower alimentary tract and not in the small intestine. The mucosa was removed from the small intestine of a recently killed dog or rabbit, and two extracts were made, one with boiling water, which does not coagulate the mucin, and the other with glycerin. Roger found that the glycerin extract contained what he calls a ferment, which will precipitate the watery extract of the mucosa after it has been purified. His interpretation of this phenomenon is, that the glycerin contains a ferment which he terms mucinase, and the aqueous extract contains mucin.

Further observations were made by Riva[9], a pupil of Roger, by Mironescu[10], and by Bruhl[11]. The inferences drawn from the experiments and observations of these authors indicate that, in the presence of a large amount of secreted mucin, there is also a mucinase secreted, and this mucinase can be identified in the serum of patients who suffer from this mucomembranous phenomenon whether it is located in the bronchi or intestine or uterus.

This work requires confirmation, but it is interesting in view of the observation which has been made by a good many writers that the mucomembranous deposits in the lung and intestines and uterus have something in common. That the pathology of the disease is independent of infection and any known kind of inflammation, but is directly dependent upon an abnormal secretory function in the mucous membrane, seems pretty well established.

Search of the literature fails to show any case of mucomembranous bronchitis which has not been preceded by some complicating disease. There are a few instances where the casts were expectorated without accompanying symptoms and apparently out of a clear sky, but these patients all gave histories of some preceding disease of the lung which could be regarded as the basic cause of the phenomenon.

There is no specific treatment which can be employed. The disease gives no symptoms excepting those which attend the expectoration of the cast, and after the cast has been ejected, there are no symptoms which remain. The only rational treatment which is conceivable must be directed toward the treatment of the basic disease, prevention of the secretory phenomenon, or the coagulation of the mucin. At present there is no method of treatment available which can be directed against the secretory or coagulation phenomena.

BRONCHIECTASIS

Bronchiectasis is a pathological lesion commonly treated as a disease. There is some justification for this treatment of the subject, because the simple fact of dilatation of a bronchus, attended with inflammation of its wall, will give a series of characteristic clinical symptoms. It is not clear just what minimum lesion of a bronchus is requisite to produce dilatation. Dilatation of the bronchus certainly does occur in syphilis, tuberculosis, necrosis of the wall of the bronchus, and destructive inflammation of the bronchial wall from any cause. There have been a few cases reported in which observers suspected that localized endobronchial disease was attended with dilatation of the bronchial tube. That loss of muscular tissue and loss of cartilage occurs in the pronounced cases, is perfectly clear, but the few reported cases of acute bronchiectasis accompanying localized endobronchitis without destructive lesions have been looked upon with a great deal of skepticism. It is possible that some of these cases which have been reported are really cases of limited congenital bronchiectasis on which an infection has been implanted. However, in the 1918-1919 epidemic of influenza bronchiectasis was found quite often in association with other pulmonary lesions, and here it seems reasonable to suppose that the bronchiectasis was acute in the sense that it had developed as a result of the recent pulmonary lesion of the influenzal attack.

Mechanism of Bronchiectasis

Bronchiectasis is a common accompaniment of interstitial fibroid disease of the lung. The bronchial dilatation is looked upon as a traction diverticulum produced by contraction of the surrounding pulmonary parenchyma. Whether this explanation is correct or not is doubtful, because we find many instances of severe interstitial fibroid disease with great retraction of the lung and no evidences of dilatation of the bronchus. If inflammatory tissue around the bronchi undergoes organization and retraction, it causes displacement of the neighboring structures; the diaphragm may ascend or the mediastinum be displaced, or indeed the costal wall may be retracted. All of these displacements are seen in chronic disease where there is no evidence of bronchiectasis. It seems probable that, in cases of bronchiectasis accompanying fibroid disease, destructive inflammatory process of the bronchial wall is the primary lesion. That the idea of a traction diverticulum may have some merit can be granted, but it is not susceptible of direct proof.

There are two other factors which may enter into bronchiectasis. One is traction on the bronchi from inspiratory movement of the thorax, and the other is an increase of endobronchial pressure which accompanies efforts at coughing. That the endobronchial pressure is raised with the effort of coughing is evident enough, but if endobronchial pressure is to explain bronchiectasis, then extrabronchial pressure over the site of bronchiectasis must be very much less than the endobronchial pressure during the act of coughing. If endobronchial pressure does not exceed extrabronchial pressure in the expiratory effort, the act of coughing could not contribute to dilatation of the bronchi.

Thus far there has been no perfectly satisfactory evidence to show just what the relations between endobronchial and extrabronchial pressure may be during an expiratory effort with a closed glottis. A normal person can produce a higher positive than negative pressure within the trachea, but we know that the high positive pressure which we can produce, as shown by blowing into a mercury manometer, is produced by the powerful abdominal muscles which, by their contraction, drive the diaphragm upward and pull the lower six ribs violently downward. The most of the compression which produces the high positive pressure is really applied over the lower and antero-lateral portion of the thorax. If the posterior and upper portions of the lung are not equally compressed during the forced expiratory movement, then the air contained within the bronchi and air spaces will cause a distention of their walls in the posterior aspects and in the apices of the lung.

However, pathological experience does not bear out this explanation for emphysema and dilated bronchi. If emphysema and bronchiectasis always occurred earliest in those portions of the lung where direct compression is not applied, we would have a simple explanation of all these phenomena. But experience shows that bronchiectasis and emphysema occur earlier in those portions of the lung where extrapulmonic pressure is applied than in parts where the mechanism for direct pressure is not so favorably disposed.

Stenosis of an affected bronchus on the proximal side of the dilatation has been employed to explain bronchiectasis by aspiration or by inspiration. If minus pressure is to explain bronchial dilatation, then there must be, over the affected bronchial segment, a minus pressure in excess of the minus pressure which is applied elsewhere over the bronchial tree, or the affected segment must sustain a diminished resistance to bursting tension. This conception of the physics of bronchiectasis is more conceivable than positive endobronchial pressure from coughing.

Diagnosis of Bronchiectasis

The writer has never had the opportunity to prove bronchiectasis on any other than inferential grounds. The X-ray pictures in some cases seem to show evidences of dilated bronchus, but I have not met with success with this method in cases which have come under my own observation. Periodical expectoration of a large amount of mucopurulent material which was accumulated over a long period within the bronchus is about the only evidence on which the diagnosis is generally made. With retention of secretion in a dilated pocket, there is opportunity for infection with numerous organisms, and also opportunities for the sputum to become fetid in character. If a dilated bronchus is located within consolidated lung, physical examination may reveal all the evidences of a cavity; but whether the cavity originates from a bronchus or from the lung is not susceptible of direct proof on physical examination. If the diagnosis of bronchiectasis within an area of indurated lung is made, it must rest entirely on inferential evidences and not on direct signs which can be elicited from the dilated bronchus.

Treatment of Bronchiectasis

There is no specific treatment for bronchiectasis. If the original cause of bronchiectasis should be a syphilitic inflammation, then antisyphilitic treatment will be of service. Otherwise the only treatment of value will be that directed against fetidity. The most satisfactory treatment for this purpose is inhalation of turpentine fumes administered by pouring a teaspoonful of turpentine on a quart of boiling water.

SYPHILITIC BRONCHITIS

Every variety of bronchitis may be simulated by syphilis. We may have the picture of ulcerating bronchitis, acute and chronic peribronchitis, bronchiectasis, and diffuse bronchitis involving the large bronchi and remote ramifications of the bronchial tree. The disease may run a very acute course or may be very chronic. There are all the possible variations in time and severity which this infection exhibits in other organs of the body. In cases of older lesions, where adventitious infection is added to the symptoms produced by syphilis, the diagnosis may be very difficult and is likely to be forgotten, but there are a few points about the syphilitic bronchitis which may suggest the specific infection.

Hemoptysis, severe, gushing, unpreceded by cough and not followed by cough, should give rise to suspicion of syphilitic origin. These cases show very slight impairment of resonance and excursion of the lung, with no modification of the character of the respiratory sound and without adventitious sounds, but the patient will give a history of recurring profuse hemoptysis that comes on without warning, and after the danger of the severe hemoptysis will have passed, all symptoms will have disappeared. The writer recalls two such experiences, both of them in women, one a woman of fifty-five years and the other forty years of age. So far as the physical signs in the lung were concerned, the history of cough and expectoration or of infection of the air passages, there was nothing to justify the expectation of severe hemoptysis. Both of these women nearly suffocated on several occasions from very acute hemorrhage into the bronchi, and both of them made complete recoveries after they were put on antisyphilitic treatment. So that recurring severe hemoptysis, unaccompanied by the usual symptoms of bronchitis, should always give rise to suspicion of syphilis as the cause.

The following case of acute mucopurulent syphilitic bronchitis simulated acute diffuse pulmonary tuberculosis. The patient was a young man, thirty years of age, with an evening rise of temperature of 101, night sweats, persistent cough, and profuse expectoration of hemorrhagic sputum, with about an equal admixture of mucus and pus. Coarse and fine mucous râles were abundant over both lungs in the upper and lower lobes. The sputum, when carefully collected, proved to be sterile; it contained no tubercle bacilli or other bacteria. A vigorous antisyphilitic treatment resulted in immediate recovery. This patient had been ill for about two months, and was preparing to go to Colorado on account of supposed acute tuberculosis.

Owing to the fact that tuberculous infections of the respiratory path occur very frequently in syphilitic patients, the serum reactions are of little aid. That a patient has a positive Wassermann reaction in his blood does not prove that his bronchial disease is syphilitic; so that, after all our modern methods of diagnosis, we are left to our clinical estimate and the therapeutic test to make the final diagnosis. As has been said, in the old cases where there has been ample opportunity for adventitious infection, the diagnosis is difficult and the therapeutic test is less satisfactory, but the two varieties just mentioned—namely, the hemorrhagic variety without other signs of bronchitis and the profuse bronchorrheal variety with sterile sputum—should arouse the suspicion of the doctor sufficiently to employ the therapeutic test.

The writer has been particularly alert to the possibility of syphilitic infections in the lungs on account of an experience during his medical student days. A colleague, who suddenly developed hemoptysis, was advised by an eminent medical authority to go to a tuberculosis sanatorium, where he spent three months without improvement, and then returned to the University hospital, where he died in the course of a few weeks. The autopsy revealed an acute syphilitic disease of the bronchial tree and pulmonary parenchyma. The tragic result of this diagnostic error has always been in mind, but in the course of twenty-five years of private and hospital practice, it has led to the satisfactory diagnosis of syphilis in only four cases.

It seems strange that the bronchial tree should enjoy comparative immunity to an organism against which no other organ of the body seems to have any particular defense. Tuberculous lesions of the upper air passages are very common, and tuberculous ulcers in the trachea and bronchi, and tuberculous peribronchitis are extremely common. If the upper air passages are to enjoy any particular defense against invading organisms, that provision consists in protection against air-borne infections, and all of the students of tuberculosis seem to be agreed that tuberculous infections of the upper air passages are acquired by inhalation. In the case of the tubercle bacillus the defense is certainly feeble. This is a rather surprising inconsistency, when we consider that syphilitic infections of the air passages are very uncommon and occur by way of the blood path, against which mode of infection there is no apparent reason for the bronchial tree to enjoy particular immunity. Certainly, when we consider the manner of infection and frequency of occurrence of tuberculosis and syphilis of the bronchi, the comparative frequency of the two infections is quite the reverse of what we would expect. The diagnosis of tuberculous bronchitis cannot be based upon physical signs alone, and it is only endoscopic examination and detection of the tubercle bacillus in the sputum that will enable us to make a diagnosis on direct evidence. Otherwise the diagnosis must be arrived at inferentially from the collective evidence in the symptoms and progress of the disease.

The Spirochaeta Castellani

This spirochete was first described by Castellani from Ceylon in 1905. The specific character of this bronchitis has been confirmed by a number of authors, and, as pointed out by Castellani, the acute hemorrhagic cases may be easily mistaken for tuberculous bronchitis. Castellani says there may be a great variation in the severity of the acute stage and the duration of the chronic period. The amount of the sputum is not large; it is mucopurulent, tinged with blood; and sometimes hemoptysis occurs quite the same as in early tuberculous cases. In fact, the sputum may be quite like any variety of sputum found in tuberculous bronchitis. Many of the patients give a clinical history of anorexia, malaise, fever, night sweats and hemoptysis. Ultimately these patients may develop extensive infections of the air cells with symptoms of bronchopneumonia, as found in cases of pneumococcus infection.

Hemorrhagic bronchitis seems to be the essential sign. Rothwell[12] described two cases with acute onset, high fever, no evidences of pulmonary consolidation, and an abundance of frothy, bloody sputum, which was loaded with Vincent's spirochete in symbiosis with the fusiform bacillus Rothwell believes that we have here the same infection of the bronchi that is commonly found in the throat, and believes the spirochete to be identical with the organism which causes Vincent's angina. There is a well recognized symbiosis of the fusiform bacillus and Vincent's spirochete that has been found in infections received from bites and also in abscesses in the vicinity of carious teeth. The clinical description of these patients reminds one strongly of what was known many years ago in France as

Woillez's disease, an acute inflammation of the bronchial path which has been ascribed to the pneumococcus.

J. W. Scott MacFie[13] described several instances of this disease. The sputum contained no pneumococci or tubercle bacilli, but very many spirochetes which resembled those found in the mouth of the patient. The point of view of several writers seems to be that the organism is one that enjoys a saprophytic existence in the mouths of these patients, and for some unaccountable reason takes on a pathogenic role in the production of severe hemorrhagic inflammation of the tracheo-bronchial path.

G. de la Mare[14] claims that the spirochete is the same one described by Vincent, and he also asserts it is unimportant whether or not it grows in symbiosis with the fusiform bacillus. The clinical signs are essentially those of tracheo-bronchitis, and may be unilateral or bilateral. According to de la Mare, the apex or base of the lungs may reveal the physical signs, and should the process extend beyond the bronchi, there may be some evidences of alteration in the density of the lung. These spirochete infections described by de la Mare were acquired at Marseilles and Bordeaux. They had a duration varying from a few days to two months in the acute form and one of them is described as having lasted six years with many periods of remission.

All the authors unite in saying that arsenic is very efficacious when given in the form of salvarsan, Fowler's solution or sodium cacodylate. Emetin given hypodermically has been found to be valueless.

Non-specific Tracheo-bronchitis

Tracheo-bronchitis is a clinical entity which remains differentiated from pneumonitis quite as clearly as cellulitis or lymphangitis of an extremity may remain a local disease. Lymphangitis may remain a local disease or may be attended with every grade of systemic reaction and systemic invasion. Analogous relations exist among bronchitis, pneumonitis and systemic invasions. The affection may begin and persist for varying periods as a localized bronchial inflammation. Systemic reactions and systemic bacterial invasions may accompany the disease while the inflammation is localized in the bronchi, but the disease frequently remains bronchial for its whole duration.

Pleurisy is a common accompaniment of bronchitis when the air cells are not invaded. The anatomical distribution of the lymphatics may be responsible for this. The bronchial tree and pleurae are supplied with lymph vessels, but none have been demonstrated in the walls of the air cells or the respiratory units. That part of the lung which contains the respiratory membrane has no lymph vessels, whereas the pleurae and that part which includes the dead space of the respiratory path are richly supplied with lymph channels. The clinical differentiation between lymphatic infection and endovascular infection strongly suggests the clinical differentiation between bronchitis and pneumonitis. Progress toward the conception of pneumonia as primarily a blood infection is much like the progress of former years from the idea of typhoid fever as an intestinal infection to the idea of a primary blood infection. Cytological and bacteriological evidence has thus far not contributed to clinical differentiation of these diseases of the respiratory path. Nosological symptoms and physical signs from the involved organs do afford many evidences for determining when the disease is confined to the dead space and when the true respiratory area is invaded.

There is a large number of cases in clinical practice whose pathogeny remains obscure. They are still classified under the general term of bronchitis, because the bacteria found in the secretions fail to satisfy bacteriological criticism. It is impossible to determine in a large proportion of bronchitides when a given organism plays a saprophytic or a pathological part, and in many instances it seems the bronchial inflammation may develop without the aid of bacteria, or the bacteria may play only a contributory role. The bronchial mucosa, it seems, may be swollen and its secretions much increased from hyperemia due to the presence of some noxious chemical content of the blood, as in gout, or the hyperemia may follow chilling of the body surface. Even in these instances bacteria come into the field either as saprophytes or as pathogenic organisms.

Swollen bronchial mucosa may encroach sufficiently on the lumina of the tubes to simulate bronchiolar hypertonus of a lobe or of the entire lung. In rare instances the main bronchus to either lung, or indeed the trachea, may be obstructed by edema of the mucosa. Such tracheal and bronchial edema was commonly seen during the influenza of 1918. In the course of chronic bronchitis acute hyperemia of the bronchial mucosa may arise with the same suddenness that bronchiolar hypertonus occurs and may be very misleading. The patients complain bitterly of discomfort in the thorax, and will clamor for breath like an asthmatic. The cough is severe and a small amount of bloody mucus is expectorated. One such patient complained more during such an attack than he was in the habit of doing in his bronchiolar spasms. Adrenalin gave no relief, and there was no inspiratory narrowing of the costal angle, as always occurred during the attacks of bronchiolar hypertonus. A hypodermic injection of apomorphin was followed by vomiting and instant relief. This is interesting in view of the old practice of inducing emesis by ipecac. It seems the splanchnic arterial relaxation which attends nausea and vomiting has a favorable effect on hyperemia of the bronchial mucosa, and the results are quite the same whether apomorphin or ipecac is employed.

When moisture occurs in large amounts in the bronchial tree, the patient will show signs of anoxemia by the color of the finger nails, ears, lips and nose, and also by elevation of the roots of the finger nails. The nail floats on its matrix, becomes quite mobile, and gives an olive-shaped finger end known as "drumstick finger tip."

Treatment of Non-specific Tracheo-bronchitis

Non-specific bronchitis must necessarily be treated from a symptomatic standpoint and not from an etiological basis. There is little to be expected from the use of drugs. In the writer's experience, therapy has never amounted to more than palliative effects. Inhalation of steam laden with the fumes of benzoin, camphor or menthol allays some of the irritation and facilitates expectoration of the bronchial secretion. When the cough is excessive and not attended with expectoration, codein, heroin, opium, or Dover's powder may be used for a brief period, but opium and its derivatives must be used with caution on account of the readily acquired habit. Compound tincture of benzoin is best employed in a steam atomizer, while menthol and camphor can be best applied by using an oil atomizer through the nostrils. Camphor and menthol, 2 grains (0.15 gram) to the ounce (30 c.c.) of albolene, is a very serviceable preparation. The spray can be inhaled so as to reach the entire bronchial tree, and gives great relief when the bronchial secretion is tenacious. Such treatment serves much better as an expectorant than the internal use of any drugs.

In the writer's experience vaccines have been very disappointing. They have been, in fact, quite useless. Until our information concerning vaccine therapy shall have been improved and the etiology of bronchitis better understood, it is advisable to refrain from the use of vaccines.

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CHAPTER II

RESPIRATORY EXCURSION OF THE THORAX

By C. F. HOOVER

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Introduction

Nearly all the methods we employ in physical diagnosis of the lungs are directed toward the study of three physical attributes: volume, density and extensibility. The present chapter will deal only with extensibility of the lungs. It is the attribute which is first modified by all diseases of the respiratory tract, and is the first attribute which will show signs of modification. In fact, modification of extensibility by disease of the respiratory structure may be plainly demonstrable long before any changes in density or volume will occur. Extensibility of the lungs is accomplished in three dimensions. Inspiratory extension of the lung is synchronously accomplished in three dimensions. Although extension is simultaneous in all parts, the extension is not *en masse*, as though the entire lung were one large elastic bag. Because a patient inspires 600 c.c. of air with each inspiration, it by no means implies an equal distribution among the several million air cells of the lungs. The uniformity of distribution will depend on the integrity of the structure and accessibility of the respiratory units, which may be modified by any disease of the respiratory structure. Ventilation of any part of the lung will also depend on functional excursion of the overlying ribs and subjacent diaphragm. As will be shown in the following discussion, not only may pulmonary ventilation be very unequally distributed in the respiratory units through disease of the intrinsic pulmonary tissues and air passages, but ventilation may be greatly impaired by disease of the motor organs, namely, the intercostal muscles, diaphragm and scaleni. Furthermore, the phase of excursion in which ventilation occurs will modify the effectiveness of a given volume of ventilation. To procure the optimum ventilation by the inspiration of 600 c.c. of air, demands that the 600 c.c. of air shall be uniformly distributed throughout the respiratory area. Any part of the lung which fails to receive its portion of tidal air will contribute unrespired blood to the aortic stream, and in proportion to the amount of unrespired effluent blood, which is contributed to the left heart by a portion of lung, the other parts of the lung must compensate by superventilation. Superventilation of one part of the lung will compensate for carbon dioxide excess contributed to the aortic stream from an unventilated part of the lung, but superventilation of one part cannot compensate for the contributed anoxemia which comes from an unventilated area. The normal lung is an exquisite tonometer, but to insure a tonometric function which will justify an inference that alveolar air is in tonometric equilibrium with effluent blood from the lung demands uniformity in ventilation throughout the lung, a normal respiratory membrane, and a normal blood flow.

The gross subdivisions of the lung usually employed are superior and inferior lobes. Anterior and posterior lobes would be an equally good, if not better, descriptive nomenclature. This is from an anatomical basis; functionally the denominations anterior and posterior lobes are well justified.

Respiratory Movements of the Upper Thorax

The mechanism for ventilation of the anterior or upper lobes is provided by action of the scaleni and intercostal muscles

The function of the scaleni is to anchor the first ribs, from which the first intercostal muscles have their origin. The scaleni do not elevate the first ribs during normal inspiration. The second ribs are elevated by intercostal muscles, and so are all the lower ribs elevated by action of the intercostal muscles. A case which I reported was that of a child, four years old, who had complete paralysis of all muscles leading from the head and neck to the thorax. Inspiration in the child had a very unusual appearance. With each inspiration the first and second and third ribs and the entire manubrium were drawn in a caudal direction, so that during every inspiration there certainly was a distinct diminution in volume of the apex of each lung. The fourth rib was stationary, and all the ribs below the fourth had an exaggerated bucket-handle movement. The subcostal angle was excessively widened during inspiration, and the hypochondria flared from the median line to an exaggerated degree. There was also an excessive protrusion of the abdominal wall. So my impression at the time was that there was an overcompensation of excursion in the lower portions of the lung for the want of normal respiratory excursion at the apices.

To confirm the interpretation of movement of the upper ribs and manubrium, a number of experiments were carried out on dogs, by means of which it was shown that we could reproduce exactly the respiratory movements in this child by cutting away the insertions of the scaleni to the upper ribs. In the course of these experiments, when the manubrium was fixed by grasping it with the forceps, the animal had perfectly normal inspiratory elevation of all the ribs, and when the anchorage of the manubrium was loosened, the respiratory movements seen in the child were again reproduced. It seemed clear from clinical and experimental experience that when the first ribs were not fixed by the scaleni, inspiratory excursion, which was gained normally by the bucket-handle movement of the second, third, and fourth ribs, was lost. In fact, instead of the lung apices being distended during inspiration, they were actually diminished in volume.

The real significance of this strange inspiratory excursion did not dawn upon me until a later experience. A child, two and one-half years old, was under the care of a surgeon who suspected some obstruction in the upper air passages. When the child lay at rest in bed, it breathed very comfortably and had a perfectly normal color. If the child were engaged in play or cried, in fact, if there were the slightest call upon the respiratory function beyond the requirements of absolute physical quiet, there was exhibited a vicious respiratory excursion. The child would develop symptoms of suffocation, breathed with very great rapidity, and developed a pronounced cyanosis; in fact, the harder the child endeavored to breathe, the worse it breathed, the more ineffective attempts at breathing became and the deeper the cyanosis grew. Unlike the first child described, the manubrium and first ribs were fixed, but there was a marked retraction from the second to the sixth rib on both sides. The seventh rib remained immobile during inspiration, but from the eighth rib down there was a violent excursion. Inspiratory protrusion of the abdominal wall was excessive, the hypochondria had an exaggerated flaring, and there was a veritable seesaw between the upper and the lower thorax. During the periods of respiratory distress there was no prolongation of either inspiration or expiration; in fact, both phases were very much shorter than normal. The child breathed as often as sixty times a minute.

Physical examination and the X-ray both failed to reveal any sign of disease of the contents of the thorax. The mediastinum, heart and lungs gave perfectly normal shadows. However, the X-ray picture did reveal extensive tuberculosis of the upper six dorsal vertebrae. The functional picture of this child was paralysis of the upper six intercostal muscles of both sides. I was unable, however, to demonstrate any sign of disease of the intercostal nerves. So far as our clinical observations went, we were forced to the conclusion that tuberculosis of the upper six dorsal vertebrae was responsible for paralysis of the upper six intercostal muscles, and beyond this nothing of a neurological character was demonstrable. The vicious respiratory mechanism in this child caused rebreathing between the upper and lower lungs. During inspiration, the lung on both sides underlying the upper six ribs was diminished in volume, and at the same time the lower parts of the lung were distended; consequently with the descending currents of air the lower lungs were distended with fresh air and also with alveolar air from the upper lung. During expiration the lower portions of the lungs were diminished in size, and the upper lungs were enlarged. Consequently a part of the air, expelled from the lower lungs during expiration, was driven into the upper lung; so when forced respiratory efforts were made there was reciprocal rebreathing between the upper and lower lung, which resulted in suffocative symptoms and extreme cyanosis that gave rise to a suspicion of obstruction of the upper air passages. Bronchoscopic examination was made in this case, and the larynx and trachea were found to be perfectly normal.

The difference between these two cases was simply one of degree of rebreathing. In the case of the child who had paralysis of the scaleni there was evidently the same vicious cycle of breathing between the apices and the lower portions of the lung, but it was not sufficient to produce cyanosis or suffocative symptoms. It was sufficient, however, to require an exaggerated excursion of the lower lungs to compensate for the rebreathing which did exist. The real significance, however, of exaggerated basal breathing in the first child was not clear until the later experience with the child who had paralysis of the upper six intercostal muscles was studied. Isolated paralysis of the scaleni and paralysis of the upper intercostals are rare clinical experiences, but they demonstrate the importance of the fixative function of the scaleni and the function of the upper intercostals in procuring normal pulmonary ventilation.

Paralysis of the mid-costal group of muscles with the lesion confined to one side occurred in a case of syringomyelia. The intercostals from the fourth to the eighth were paretic, but over the area from the fourth to the eighth inclusive there was distinct retraction during inspiration. This patient had a very small vital lung capacity, only 1,100 c.c. In this case the small capacity could not be accounted for by disease of the lung or circulatory system. In addition to paralysis of the intercostals above mentioned, there was also demonstrable paresis of the left side of the diaphragm. The patient was constantly on the border of an anoxemia amounting to cyanosis. Very slight physical effort, in fact, would bring out cyanosis and air hunger. Impairment of the vital capacity was due to paresis of the muscles of respiration, but in addition to the paresis of the intercostals and diaphragm we had the factor of regional location of paresis, which caused rebreathing between the mid-portions of the left lung and the lower part of the left lung. These instances of paralysis of the scaleni and paralysis of the upper intercostal muscles and that of the mid-intercostals, show a striking contrast to the cases in which the paralysis is in the lower intercostals. Paralysis of the lower half of the intercostals is very well tolerated, because this does not produce rebreathing between the upper and lower lung. Patients who have transverse myelitis in the mid-dorsal region have their upper intercostals and diaphragm preserved. During inspiration there is no diminution in volume of any portion of the lung, and when there is no diminution of any portion of the lung during the inspiratory act, there can be no reciprocal rebreathing between any two pulmonary regions. When all the intercostals of one side are paralyzed the patient is not cyanotic.

A little girl, eight years old, had hemorrhage into the cervical cord following a fall to the ground from a ladder. The child had a complete paralysis of all the intercostals of the left side and complete paralysis of the diaphragm of the left side. All the intercostals and the diaphragm of the right side functionated normally. If we were to assume there was no ventilation of the left lung, then it must follow that all of the blood flowing into the left auricle from the left pulmonary veins must be venous blood. Under such conditions we certainly would have had a marked anoxemia and air hunger to compensate for the carbon dioxide contributed to the aortic stream by the unrespired blood from the left lung. Now, nothing of the kind happened. The child lay very tranquilly in bed, without the slightest sign of cyanosis. Although the respiratory rate was accelerated, there was not the least sign of respiratory discomfort. During respiration there was no retraction of the left thoracic cage. There was no rebreathing between the left and right sides. The only way, however, in which the absence of cyanosis can be explained seems to be to suppose that there must have been a lateral movement of the mediastinum, so that during inspiration the movable mediastinum must have been drawn toward the right side and moved toward the left side during expiration. In this wise, during inspiration there would be some increase in the transverse diameter of the left lung and a corresponding diminution in the transverse diameter of the right lung, but the increase in the longitudinal and anteroposterior diameters would compensate for diminution in the transverse diameter of the right side. Consequently, in this child, with complete respiratory paralysis of the whole left side, there was some ventilation of the left lung due to lateral movement of the mediastinum.

Patients who have transverse lesions of the lower cervical cord, so that the scaleni and diaphragm are the only respiratory muscles preserved, do not suffer from respiratory distress or give any evidence of anoxemia as they lie at rest in bed. When the scaleni and the intercostals are intact, paralysis of the diaphragm is very well tolerated. The patients compensate for the want of descent of the diaphragm by increasing the action of their intercostals, but there is no rebreathing between the upper and lower lung, and patients exhibit no cyanosis. It is clear that if any part of a lung is not ventilated by respiratory action, and blood flow in the pulmonary vessels through the unventilated portion continues, then of course this unventilated lung portion contributes venous blood to the aortic stream. A certain amount of unrespired blood may be contributed to the aortic stream without altering the patient's color or his respiratory comfort, but this kind of lesion does not give respiratory symptoms comparable with any lesion which will cause rebreathing between two different parts of the lung. Any loss of power in the intercostal muscles or the scaleni which will result in a diminution of a part of the lung during inspiration and consequent return to the original size during expiration, must of necessity cause reciprocal rebreathing between two different portions of lung. Such a disturbance in respiration causes very severe symptoms.

These considerations show how essential it is that the inspiratory act should be attended with an increment in all the radii of the chest cavity, for otherwise we will have either one portion of the blood contributing unrespired blood to the aortic stream or, what is still worse, there may be reciprocal rebreathing between different lung areas.

Respiratory Function of the Accessory Muscles

Increase in the anteroposterior diameter of the thorax in normal inspiration is due solely to the intercostal muscles. When the accessory muscles are employed, as in cases of asthma and emphysema, their function is expended in increasing the anteroposterior diameter of the thorax. An increment of the anteroposterior diameter of the thorax will ventilate the anterior or upper lobe, but will contribute little to ventilation of the posterior or lower lobes of the lungs. Let us assume that the patient has a vital capacity of 5,000 c.c. of air; now let bronchiolar spasm supervene, so that his vital capacity will be reduced to 1,000 c.c. This 1,000 c.c. of vital capacity under these conditions will increase the volume of the lung from 4,000 to 5,000. This vital capacity of 1,000 c.c. of air will be procured from an excursion of the lung from the position of 4,000 to 5,000, and is accomplished very largely through employment of the accessory respiratory muscles, which lift the thoracic cage and give the bellows-like movement to the thorax which ventilates the anterior or upper lobe. In other words, the asthmatic or emphysematous patient has a sufficient vital capacity to maintain him in respiratory comfort if the tidal air of the vital capacity were equally distributed throughout the entire respiratory area; and it seems quite probable that at least one of the reasons why his vital capacity is not adequate to maintain him in comfort, is the unequal distribution of the ventilating air.

The Transverse Diameter and the Intercostal Function

Inspiratory increase in the transverse diameter is accomplished entirely through the bucket-handle movement of the mid-portion of the arcs of the ribs. This begins in the axillary line at the third rib, increases to the fifth rib, is about constant from the fifth to the tenth, and diminishes from the tenth to the twelfth. The bucket-handle movement of the ribs contributes to the ventilation of the lower portion of the upper lobe, but its chief contribution is to the ventilation of the upper and mid-portions of the posterior lobe. The longitudinal diameter of the thorax is increased solely through the descent of the diaphragm. The excursion of the diaphragm is downward and forward, so that the excursion of the anterior abdominal wall is a direct measure of phrenic excursion.

Clinical Study of Lung Ventilation

In studying the respiratory excursion of the lung one must observe the ventilation of the upper or anterior lobe and ventilation of the lower or posterior lobe. If the scaleni are functioning, the manubrium and first ribs will be fixed, but the second, third, fourth and fifth ribs move simultaneously but with different degrees of excursion. The excursion of the third rib exceeds that of the second; the excursion of the fourth exceeds that of the third; and the excursion of the fifth exceeds that of the fourth. This is due to the increment of the arcs of the respective ribs, and gives an undulatory character to the movement from the second to the fifth ribs, inclusively. If the ends of the fingers of one hand are placed on the second, third, fourth and fifth ribs,—in a line drawn from the mid-clavicular line on the second rib to the anterior axillary line on the fifth rib,— the increase in the arcs of excursion will be plainly palpable and visible; and should there be any impairment in the extensibility of the lung, this succession of movement from the second to the fifth rib will be affected. Any disease of the bronchi, or pulmonary parenchyma, or pleura may impair the extensibility of the lung, and will be distinctly mirrored in a modified movement of the overlying ribs. Instead of the succession of movement which we normally see, the ribs may all move the same distance, or one or more of the ribs may be immobilized. It is true that flexibility of movement of the thorax varies in patients, but when there is any disparity in extensibility between the two sides of the lung, it can be detected with extreme nicety by this simple method of examination. Inasmuch as extensibility is the first attribute of the lungs to be modified in any disease, it becomes a very serviceable method of detecting the early stages of pulmonary invasion and is particularly valuable when the invasion is unilateral. For instance, in the early stages of tuberculosis of the apex of one lung, impairment of extensibility may be the only physical sign which we can elicit. The percussion note may not be modified and there may be no adventitious signs; in fact, there may be no physical sign to betray any change in volume or density of the lung, and impairment of extensibility will be the only demonstrable evidence of disease. For this reason routine examination of the extensibility will be the only demonstrable evidence of disease and is of very great clinical service.

Respiratory Movements of the Lower Thorax

The respiratory movements of the lower thorax have been a source of much physiological and clinical discussion since the time of Galen. Excursion of the anterior abdominal wall has always been clearly ascribable to descent of the diaphragm. The lateral movement of the ribs in the mid-portions of the costal arc is clearly due to the function of the intercostal muscles; but the inspiratory movement of the costal margins or collected ends of the ribs from the sixth to the twelfth has been a source of much debate. Finally the question seemed to have been definitely settled by Duchenne (Recherches Electro-Physiologiques et Therapeutiques sur la Diaphragme, 1853), and Duchenne's interpretation has been accepted by all writers on clinical and physiological subjects.

Duchenne found that, during inspiration, the subcostal angle widened and the costal margins moved away from the median line when the intercostal muscles were paralyzed and only the diaphragm was functionating.

He found also in experiments on dogs that when the viscera of the upper abdomen were removed, there was an inspiratory narrowing of the subcostal angle, and the entire costal margin moved toward the median line. His interpretation was that, on account of increase in intra-abdominal pressure due to descent of the diaphragm, the hypochondria were pushed in an outward direction and thus gave rise to inspiratory widening of the subcostal angle, but when the liver, spleen and stomach were removed, so that the viscera were not driven downward during the descent of the diaphragm, then the insertions of the diaphragm to the ends of the ribs caused narrowing of the subcostal angle, and the costal margins in their entire extent were drawn toward the median line. The whole difficulty of the problem lay in the fact that students of the problem, before and since the time of Duchenne, have failed to differentiate between evidence of excursion of the diaphragm and evidence of activation of the diaphragm. In all the works on anatomy and physiology we find Duchenne's interpretation accepted as final, and in all neurological works and monographs on the diaphragm the symptoms of diaphragmatic paralysis are very unsatisfactorily discussed.

The direction of movement of the costal margins has nothing to do with excursion of the diaphragm. The most obvious thing is really the truth; the outward movement of the costal margin is due to action of the intercostal muscles, and movement of the costal borders toward the median line is ascribable to activation and not to excursion of the diaphragm.

The direction which the costal margins will take during inspiration will be the resultant of the conflict between the two groups of muscles—namely, the intercostals and the diaphragm. If the diaphragm gains mastery of any part of the costal margin, then it will move toward the median line during inspiration. If the intercostal muscles gain the mastery of the costal margin, it will move away from the median line during inspiration. In a normal human subject there is a very nice balance in favor of the intercostals, so that we see under normal conditions the costal margins move laterally during inspiration.

The question which has been raised has been, why do the intercostals enjoy the balance of power so far as the movement of the costal margin is concerned. The dome of the diaphragm varies greatly in the arc of convexity in its different portions; for instance, the anteromedian or subcardial portion of the diaphragm has very much less convexity than the lateral or posterior portions of the diaphragm. The resultant line of traction from an activated fiber of the diaphragm will be a straight line drawn between the central tendon, the point of its origin, and the rib, the point of its insertion. Now it is clear that the more nearly the fibers of the diaphragm coincide with a straight line, the more effective will be their traction on the ends of the ribs during activation. And another point of importance in this relation must be mentioned, that it requires much less depression of the subcardial portions of the diaphragm than of the lateral and posterior portions to gain the mastery of the costal margins where their respective fibers are inserted; and also it must be remembered that different lesions will modify the convexity of the diaphragm in very different ways. Emphysema of both lungs will cause flattening of the entire phrenic dome. Unilateral pleurisy with effusion and pneumothorax will diminish convexity of one-half of the diaphragm. Pericarditis with effusion will flatten the entire subcardial diaphragm and leave the lateral and posterior portions unmodified. Enlargement of the left ventricle will depress the subcardial portion of the diaphragm to the left of the median line much more than to the right of the median line. Dilatation of the right ventricle and right auricle will depress the subcardial diaphragm to the right of the median line much more than to the left of the median line. Convexity of the entire diaphragm may be increased by ascites or tympanites; the right half of the diaphragm may have its convexity increased by enlargement of the liver; while the left half may have its convexity increased by tumors of the spleen or stomach. Subphrenic abscess may also increase the convexity of either side. In obsolete pleurisy there may be a shortening of the longitudinal diameter of the thorax and an increase in the concavity of the under surface of the diaphragm. But in these cases there are always synechia between the diaphragm and the chest wall, and consequently the diaphragm is given a new point of insertion; instead of being at the end of the ribs, it will be at the inner surface of the chest wall. So although the under surface of the diaphragm may have its concavity increased, there is lessened convexity of the upper surface of the effective portion of the diaphragm.

The conformation of the diaphragm will determine the direction of movement of the costal margins; consequently the movement of the costal margin gives us some indication of the conformation of the diaphragm. This is always an important point in physical diagnosis. By direct inspection we determine the conformation of the thoracic cage, but it is only by inferential procedures that we can gain any conception of the inferior boundary of the thorax, and we cannot pretend to have made a complete physical examination of the chest without forming some conception of the conformation of its inferior boundary, and this its most movable boundary.

Unlike other skeletal muscles, the diaphragm's function does not consist in approximating its origin and insertion, but in shortening the line of its arc. The resultant of a line of traction is a straight line; so the more nearly the line of the phrenic fibers coincides with a straight line, the more effective will be its traction on the costal margin. There is some inspiratory advantage in the fact that the intercostal muscles dominate the control of the costal margins. Spreading the hypochondria contributes to flattening of the diaphragm during inspiration, so that in reality whatever significance the spreading of the hypochondria may have in contributing to inspiration, this contribution is made by the intercostal muscles and not by the diaphragm. If a young, vigorous person be asked to protrude the abdomen, or, in common parlance, to "poke out his stomach," he will strongly contract his diaphragm, and then, if he is instructed to hold his abdomen in this position and make a forced inspiration, it will be seen that, during the inspiration which follows, the costal margins will be drawn toward the median line, although the second phase of excursion is performed entirely by the intercostal margins, and is not shared in at all by the diaphragm, because the diaphragm has already made its maximum descent before the intercostals are employed. During the second phase of this prescribed procedure the diaphragm is activated but does not perform any excursion. However, the diaphragm is sufficiently flattened by the initial procedure to gain mastery of the costal margin, and during the second phase, by its further activation, it will draw both costal margins toward the median line. This is a very simple method of confirming the significance of the flattening of the diaphragm in gaining mastery of the costal margin.

Movement of Costal Margins in Clinical Conditions

When the dome of the liver is enlarged by acute changes in the liver, as in granular degeneration or in acute diseases of the hepatic parenchyma, the right costal margin will be seen to move more promptly and farther in an outward direction than the left costal margin during inspiration. In other words, if the arch of the right diaphragm is increased, the balance of the power is given still further than normally to the intercostal muscles, and consequently the outward movement of the costal muscles will be accentuated during inspiration.

Subphrenic Abscess.—In cases of subphrenic abscess, this phenomenon is of particular value. The difficulty in diagnosis of subphrenic abscess lies in differentiation from thoracic empyema. In both we have dullness at the base of the thorax laterally and posteriorly, a loss of tactile fremitus, and, should there be sufficient synechia between the visceral and parietal pleura, so that the lung cannot recede from the pleural sinus as the diaphragm is pushed upward, then we shall have bronchial breathing and whispered pectoriloquy, so that inspection, percussion and auscultation in both subphrenic abscess and thoracic empyema may give exactly the same results. However, in the case of thoracic empyema, either the outward movement of the costal margin will be diminished or the inspiratory movement of the costal margin will be toward the median line; whereas in four cases of subphrenic abscess which have come under my observation, the costal margin on the right side moved farther and more actively away from the median line than did the left costal margin, on which side in each case the lung and pleura were unaffected.

Obsolete Pleurisy.—In cases of obsolete pleurisy, with synechia between the phrenic pleura and parietal pleura, the arch of the diaphragm is of course accentuated, but the effective portion of the diaphragm, so far as the movement of the hypochondria is concerned, will be that portion of the diaphragm between the central tendon and the point of fixation to the thoracic wall. This gives a new point of fixation to the diaphragm. The attachment to the costal border has no longer any significance, so far as phrenic excursion or phrenic traction is concerned. Consequently the movement of the costal margin will either be restrained or be drawn toward the median line by virtue of the thoracic insertion of the diaphragm, which converts its effective part into a plane. This can be very easily shown in an animal by suturing the diaphragm to the eighth ribs in the axillary line. Immediately this is done the costal margin will be seen to move toward the median line during inspiration, and when the suture is released the costal margin will again resume the outward movement during inspiration.

Cardiac Enlargement.—This portion of the diaphragm has a more flattened arch than the lateral and posterior portion, and therefore much less depression of this portion of the diaphragm is required to modify the movement of the costal margin than is required, in the case of the lateral and posterior portion of the diaphragm, to modify the movement of the costal margin where their fibers are inserted. If a patient has an elongated and enlarged left ventricle and the right ventricle and right auricle are not enlarged, we may see asymmetry in the movement of the subcostal angle. From the subcostal angle to the eighth costal cartilage on the left side there will be a restraint of the border, and in some instances the costal margin will move toward the median line during inspiration, whereas the right costal margin will move outward. When the enlargement of the heart is globular, as in synechia cordis, syphilitic myocarditis, and diseases of the mitral valve, we commonly see narrowing of the subcostal angle during inspiration, and the inspiratory narrowing may be symmetrical, although on both sides below and external to the eighth costal cartilage the borders will move outward during inspiration. This observation will frequently save one from the error of underestimating the size of a heart when the person is lying down. If the anteroposterior diameter of the thorax is sufficiently large and the heart mobile, the precordial area of dullness may not be enlarged, but if under such circumstances there is narrowing of the subcostal angle, one may be quite sure there is flattening of the subcardial diaphragm both to the right and left of the median line. The enlargement of the precordial area may be confirmed by percussion of the patient in the upright position and by the use of the fluoroscope.

Phosgene Poisoning.—In the acute stage of phosgene poisoning, dilatation of the right ventricle and right auricle is of frequent occurrence. The left ventricle and left auricle never dilate during this period. In acute pulmonary emphysema, which is frequently met with at this time, percussion of the right auricle to the right of the sternum is very uncertain or very difficult. Flattening of the subcardial diaphragm to the right of the median line, however, could be recognized by the fact that the right costal margin between the angle and the eighth rib was restrained in its outward movement, or it moved toward the median line during inspiration. When these patients were given as much as 1/25 of a grain (2.5 mgm.) of digitalin subcutaneously, and the right heart regained its normal size, the costal angle was seen to widen symmetrically during inspiration.

Pericarditis with Effusion.—Free fluid in the pericardial sac will cause a marked depression of the subcardial diaphragm; in fact, there is no intrathoracic disease which will cause greater downward displacement of the liver than pericarditis with effusion. If the fluid within the pericardial sac is not walled off and lies perfectly free, a considerable amount of fluid, or fluid in sufficient quantities to impede the diastole of the heart will always give a symmetrical narrowing of the subcostal angle during inspiration, and as the fluid is withdrawn we see the inspiratory narrowing converted into inspiratory widening of the costal angle. This is the phenomenon which has given rise to an error in diagnosis of paralysis of the diaphragm in pericarditis with effusion. The subcardial portion of the diaphragm with large effusion will of course not descend during inspiration, but the subcardial portion of the diaphragm is nevertheless activated and gives rise to the narrowing of the subcostal angle.

Emphysema.—Emphysema due to bronchitis, atrophic emphysema, emphysema from bronchiolar spasm, and acute emphysema from laryngeal stenosis may all cause sufficient flattening of the diaphragm so that the entire costal margin on both sides will be drawn toward the median line during inspiration. It is a common experience in chronic bronchitis with emphysema to find the lower borders of the lung sufficiently enlarged to fill the pleural sinuses. This will be true during periods of comparative comfort, when the patient is not suffering any respiratory distress and there is no cyanosis. There may be a period of bronchiolar spasm or an increase in the severity of the bronchitis. The patient will then have cyanosis and suffer from air hunger and dyspnea. So far as percussion is concerned, the conditions remain the same in the periods of acute discomfort and in the interims of euphoria. However, if one will observe the costal margins during the periods of cyanosis and dyspnea, the costal margins will be seen to move toward the median line during inspiration. This is the only physical sign which will clearly indicate an increase of volume of the entire lung during the acute attacks. The emphysema of the edges of the lung, though they may fill the pleural sinuses, will not flatten the arch sufficiently to give the diaphragm mastery over the costal borders during inspiration. However, when the great volume of lung is enlarged and the entire leaf of the diaphragm is flattened, then the diaphragm gains mastery of the entire costal margin. This point is of very considerable service in differentiating between genuine bronchiolar asthma and pseudo-asthma, both of which frequently occur in the course of chronic bronchitis with emphysema. These patients acquire such a phobia toward their attacks that pseudo-asthma becomes a very common experience. The patients cannot differentiate between the pseudo-asthma and the asthma due to bronchiolar spasm. The pleural sinus is always filled with emphysematous lung, so that percussion is of no service in differentiating between the genuine and spurious attacks. The true attacks of bronchiolar spasm are always accompanied by inspiratory retraction of the costal margins, and the behavior of the costal margins during false attacks remains just the same as during the periods of comparative comfort. I have on several occasions been able to confirm this observation by relieving the genuine attacks with hypodermic injections of adrenalin, whereas the pseudo-attacks were relieved equally well by hypodermic injections of adrenalin or water.

Emphysema Associated with Cardiac Disease.—Chronic bronchitis and emphysema associated with cardiac disease may often give rise to much difficulty in estimating the share which may be played by the cardiac disease and the share which is played by the emphysema. If the patient has cyanosis and air hunger, and inspiratory narrowing of the costal borders is seen throughout the entire costal margin, then we may be sure that the entire diaphragm is flattened, and thus the inference is justified that the total volume of both lungs is greatly increased. If, however, inspiratory narrowing of the subcostal angle and retraction of the costal borders is confined to that portion of the costal margin between the angle and the eighth rib, we know that only the subcardial portion of the diaphragm and not the entire diaphragm is flattened, and if the right diaphragm is not flattened, then the patient cannot have emphysema as a source of his cyanosis. When the costal margins to the eighth rib are involved, we are dealing with a cardiac source of air hunger and not with a pulmonary source of air hunger.

Movements of the Diaphragm

Duchenne very clearly states that when dogs have paralysis of all their intercostals and the diaphragm is alone active, the costal margins spread during inspiration. This is not true in human beings. In every case of paralysis of the intercostals which has come under my observation, when the diaphragm was still active the costal margins were drawn toward the median line during inspiration.

In 1913 I made a series of observations on dogs relative to the function of the diaphragm and the intercostals, and I always found the behavior of the costal margins in paralysis of the intercostals and paralysis of the diaphragm was exactly the same as I had observed in human subjects. In all of these experiments the abdomen was opened so that a clear view of the under surface of the diaphragm could be procured. A few years ago I repeated my observations and made sections of the lower cervical cord of a dog without opening the abdomen. I was surprised to find the costal margin spread just as Duchenne described, but the spread of the hypochondria was not of the same character and not carried out with the same vigor as is seen when the intercostal muscles are active. It was clearly a passive spread and not an active widening of the hypochondria. An incision was made in the median line, so that the abdominal cavity freely communicated with the outside air. It was then seen that the entire costal margin on both sides was drawn toward the median line during inspiration. When the incision was closed by clamps, the passive spreading of the hypochondria was again apparent.

As it happened, the first experiment was done on a setter dog, the type of dog which has a long thoracic cage and a very high arch to the diaphragm. When the abdomen of this dog was closed and the diaphragm activated, there were two forces at play on the hypochondria. One was the traction on the costal margins from the diaphragm, and the other was increased pressure in the abdominal cavity which accompanied descent of the diaphragm. The setter dog has such a high arch to his diaphragm that increase in abdominal pressure exceeded the traction on the costal margin. When, however, the abdomen was opened so that descent of the diaphragm did not increase the intra-abdominal pressure, then traction of the diaphragm on the costal margins became apparent, and both margins in their entire extent were drawn toward the median line during inspiration.

Another type of dog was then employed, the bulldog, which has a shorter thorax and a flatter diaphragm, much more like the human diaphragm than that of the setter. When the intercostal muscles were paralyzed by transsection of the cervical cord, the costal margins were drawn toward the median line when the abdomen was unopened. The bulldog's diaphragm, much like the human diaphragm, is sufficiently flat so that traction on the costal margin will overcome the increased lateral pressure produced by descent of the diaphragm.

Duchenne and his contemporaries who did the same experiment do not describe the type of dog used, but from their conflicting results, it is very probable, in the light of my own experiments, that Duchenne used the setter type of dog, and some of his contemporaries who got other results, evidently used a bulldog type.

There are other clinical experiences which clearly refute Duchenne's interpretation of diaphragmatic phenomena. I have observed three cases of large empyema in the left pleural cavity, in all of which the spleen was displaced below the costal margin. The percussion note was flat from the clavicle to the costal margin, and, much to my surprise, in the first of these patients the costal margin on the affected side moved away from the median line during inspiration, although not so far as the right costal margin. The idea then occurred that the diaphragm was convex on its under surface and for this reason lost control of the costal margin. Two pints of pus were withdrawn from the pleural cavity with a Potain aspirator. Then the costal margin was seen to move strongly toward the median line during inspiration. The diaphragm was sufficiently elevated to gain control of the costal margin. Then three pints more of pus were aspirated and the costal margin again moved away from the median line during inspiration. Thus the diaphragm became sufficiently elevated so that it lost control of the costal margin. We have here a very excellent proof that the determining factor in the movement of the costal margin does not lie in elevation or depression of the diaphragm, but in its convexity and flattening, and it is quite the same whether it is convex on the under surface or on the upper surface. In both cases it will lose control of the costal margin.

In a recent case of pressure hydropneumothorax of the right side, with the fluoroscope we could clearly see the concavity of the upper surface of the diaphragm, and the diaphragm could be clearly seen to rise during inspiration. The right costal margin moved away from the median line, although the liver was of course seen to rise instead of descend during inspiration. When air was released from the pleural cavity so that barometric pressure prevailed in the pleural cavity, the costal margin was drawn toward the median line during inspiration.

The Litten Diaphragm Phenomenon

The diaphragm phenomenon described by Litten consists of a visible band of retraction which occupies the pleural sinus and includes both costal and intercostal spaces; thus, both the ribs and the intercostal spaces are seen to be retracted over the pleural sinus. In the beginning of the inspiratory movement this initial band of retraction is due to activation of the diaphragm which precedes excursion. As excursion of the diaphragm proceeds, the band of retraction is erased by a descending shadow, which marks the descent of the lower border of the lung into the pleural sinus as the diaphragm is withdrawn from the thoracic wall. So that we may speak of the band of retraction in Litten's phenomenon as due to activation of the diaphragm, and erasure of the band of retraction as due to excursion of the diaphragm. If we are to sum up the visible evidence of activation of the diaphragm under normal conditions, Litten's band of retraction is the only visible evidence. Evidences of activation of the diaphragm, so far as the costal margin is concerned, become apparent only with flattening of the phrenic arch. Visible evidences of excursion of the diaphragm are the erasure of the band of retraction, as described by Litten, and protrusion of the anterior abdominal wall.

The direction of movement and symmetry or asymmetry of movement of the costal margins are very considerable aids in estimating the following conditions: (1) conformation of the heart; (2) the size of the pericardial sac; (3) the volume of the lung; (4) differentiation between pleurisy and pneumonia; (5) obsolete pleurisy; (6) enlargement of the liver; (7) subphrenic abscess; (8) pneumothorax; (9) paresis of intercostal muscles and diaphragm.

It must not be understood that the direction of movement of the costal margins is diagnostic or pathognomonic of any of the above mentioned diseases. The movement of the costal margin simply gives us evidence of the conformation of the vault of the diaphragm. One may have pleurisy with effusion or a hemothorax without flattening of the diaphragm, and in fact there may be a slight pneumothorax without demonstrable phrenic flattening; and there may be great enlargement of the heart with little or no depression of the subcardial portion of the diaphragm, if there should be an accompanying ascites or any other intra-abdominal lesion which would prevent descent of the diaphragm. The practical diagnostic point is simply this: in making a physical examination, we must not merely study the excursion of all the ribs but we must consider the symmetry or asymmetry of excursion of the costal margins, and the direction and degree in which they move, and we must also study the movement of the upper and internal portion of the costal margin as compared with that of the lower and external margin of the same side. When the excursions of the costal margins are studied in this manner, it will often lead to suggestion of pathological lesions which otherwise would not be suspected, and it will often give us information on the contour of the diaphragm which is otherwise quite neglected. This method of studying the diaphragm gives us information which even the X-ray and fluoroscope fail to give, for the X-ray simply gives us a silhouette of the projected dome of the diaphragm, and does not give us accurate information on the curvature and function of different parts.

Hernia of the Diaphragm

Hernia does not modify the movement of the costal margin or protrusion of the anterior abdominal wall during inspiration.

Recently a man with a large hernia of the stomach through the left diaphragm, which the patient had carried for many years, presented the following objective signs: the volumes of the two sides of the thorax were symmetrical; over the left base and infrascapular and lower axillary region there were distinct dullness, diminution in tactile fremitus, and elevation in the pitch of the respiratory sounds; an intrathoracic succussion was clearly demonstrable; there was no coin sound. In spite of these signs, however, it was observed that the costal margin on the left side retained a perfectly symmetrical movement with the costal margin of the right side. This fact alone gave rise to suspicion of a hernia of the diaphragm. In fact I can conceive of no other condition which would give the described intrathoracic signs and not modify the movement of the costal margin. The diagnosis was easily confirmed by giving the patient a barium meal, which was swallowed under observation with the fluoroscope.

SUMMARY

Routine examination of patients should include careful observations on the manner of movement of the costal margins. The direction in which that part of the costal margin may move which lies between the subcostal angle and the eighth rib, should be studied in comparison with the movement of the lower and outer portion of the costal margins; and the symmetry or asymmetry of movement of the two borders in their inner and outer portions should be determined.

Should any part or all of both costal margins move toward the median line during inspiration, then the diaphragm attached has gained mastery over the opposing intercostal muscles, because: (1) the involved diaphragm is flattened; (2) the opposing intercostal muscles are paretic; (3) there are synechiae between the diaphragm and the inner surface of the chest wall, thus giving a new insertion of the diaphragm. Should the costal margin of the affected side move farther outward than the costal margin of the normal side, then traction on the costal border from activation of the diaphragm has been lessened, either because of an impairment of muscular power or because the phrenic arch has been elevated and the disparity between the curve of the effective muscle fibers and line of traction has been increased.

Should the costal margin of one side show lessened movement but in an outward direction, then there may be: (1) partial loss of domination of the costal margin by the intercostals due to moderate flattening of the phrenic arch; (2) any lesion which will impair extensibility of the lower part of the lung and thus retard excursion of the ribs; (3) restraint of the costal margins due to spasm of the abdominal muscles.

Excursion of the costal borders can be studied only when the patient is lying down with all abdominal muscles relaxed. In the upright position the abdominal muscles restrain the outward movement of the costal margins. The borders should be carefully palpated in their entire extent, and movement related to the median line must be carefully differentiated from movement anteriorly and upward. It is only movement laterally and toward the median line which concerns the balance between the diaphragm and intercostal muscles.

This method of studying thoracic excursion has been of very great diagnostic aid, and has greatly enhanced the interest in cardiorespiratory as well as nervous diseases and diseases of the upper abdomen.

CHAPTER III

DISEASES OF THE LUNGS

By LOUIS HAMMAN

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DISEASES DUE TO CIRCULATORY CHANGES

PULMONARY CONGESTION

It is customary to distinguish active and passive congestion of the lung. Neither condition can be regarded as a pulmonary disease since they are both secondary to other conditions. However, passive congestion is associated with a definite group of symptoms, whereas active congestion adds nothing of importance to the symptoms of the underlying disease.

Active Congestion

Active congestion or hyperemia is associated with every inflammatory disease of the lungs and scarcely deserves any separate mention. The most striking type of hyperemia is the stage of engorgement in lobar pneumonia. French authors under the name of Woillez' disease have described a form of pulmonary congestion characterized by a short period of fever, cough and sputum, a little impairment of the percussion note, diminished or slightly blowing breath sounds and fine moist râles. The symptoms are mild and end in recovery. Cultures from the sputa and lung puncture material have demonstrated in nearly all instances the pneumococcus, which is supposed from animal experiments to be an attenuated form of pneumococcus. These cases have all the characters of a mild or abortive pneumonia and should properly be considered under that heading. In some of the acute specific infections frequently complicated by pneumonia death may occur while the lungs are intensely congested and before much exudation has occurred, a condition to which the name "hemorrhagic pneumonitis" has been given.

Passive Congestion

Passive congestion is always the result of obstruction to the blood flow in the pulmonary circulation. The commonest cause is disease of the mitral valves, but it occurs frequently in aortic insufficiency, myocardial disease and in myocardial insufficiency from whatever cause. In passive congestion the lungs feel tough and resistant, and the cut surface is red. The capillaries are engorged and distended, and project as loops into the alveolar spaces. The term *"red induration"* has been applied to this condition. If the congestion lasts for a long time the lungs become thickened and indurated, due to the growth of connective tissue in the alveolar walls, and they acquire a brown color from the deposition of pigments derived from the hemoglobin of destroyed red blood corpuscles. This condition is described as *"brown induration."* The alveoli contain degenerated epithelial cells, red blood corpuscles, a few leukocytes and large round cells filled with brown pigment granules, the cells commonly called heart-failure cells. There is a varying amount of serous fluid in the alveoli. The bronchial walls are congested and the mucous membranes often a little swollen.

The *symptoms of chronic passive congestion* are dyspnea, cough and sputum. The dyspnea depends mainly upon the unsatisfactory blood flow in the pulmonary circulation and varies with the myocardial efficiency. In late stages of passive congestion the lungs lose their resiliency and become added factors in the dyspnea by making ventilation more difficult, and by depriving the pulmonary circulation of the aid rendered by the suction of the expanding lung.

Cough varies with the intensity of the congestion and the degree of bronchial inflammation. In congestion of long standing, bronchitis is always associated, and it not only causes cough, often of a most harrassing character, but if severe, further complicates the situation by causing pulmonary distension.

The sputum varies in amount and character. The associated bronchitis gives it a mucopurulent character; but it is richer in albumin than the sputum of simple bronchitis because of the admixture of serous exudate from the alveoli. The sputum often contains streaks or flecks of bright blood, but is more commonly of a yellowish red tone with spots of deeper rusty brown color. This coloring is given by the iron-containing pigments of altered hemoglobin. Microscopical examination discloses the characteristic "heart-failure cells."

The *physical examination* of the lungs shows little change on percussion. The pulmonary distension may give an increased resistance to percussion and a hyperresonant quality to the note. The pulmonary excursion is limited. The breath sounds are often diminished in intensity, especially over the lower lobes; they may be harsh and roughened. Fine moist râles are heard over the bases, and frequently sonorous and sibilant râles, generally distributed.

The X-ray picture is often distinctive. The hylus shadows are deepened and widened; the lung fields cast a deeper shadow than normally; and the shadow of the ramifications of the bronchial tree is very wide and deep. These shadows are cast by the distended pulmonary vessels.

Diagnosis.—There is seldom difficulty in diagnosing pulmonary congestion because the cardiac condition to which it is secondary is usually obvious. However, the symptoms are occasionally misinterpreted. The clinical history of mitral stenosis is often strikingly like that of pulmonary tuberculosis: severe cough, profuse sputum, shortness of breath, recurring hemoptysis, often loss of weight and a little fever. I have seen good physicians overlook the mitral stenosis, and such cases are occasionally sent to tuberculosis sanatoriums. In emphysema and chronic bronchitis myocardial insufficiency gradually develops, and when patients are observed for the first time in the stage of severe myocardial insufficiency, the pulmonary symptoms are often ascribed to congestion alone, and the cardiac condition is regarded as the primary disease. The true sequence of events may be unsuspected until autopsy reveals the absence of valvular and myocardial disease and the presence of tremendous hypertrophy and dilatation of the right heart.

The treatment of passive congestion is the treatment of the underlying cardiac condition together with the usual remedies employed to mitigate the symptoms of the associated bronchitis.

Hypostatic Congestion

In patients with weakened heart action who remain for a long time in one position, congestion occurs in the dependent parts of the lungs, and serum exudes into the alveoli. The same conditions favor the development of areas of atelectasis, and the combination of edema and atelectasis gives the typical picture of hypostatic congestion. The lungs become firm and tough, and the alveoli filled with a serosanguinolent exudate that gives the affected parts a deep brownish red color, the consistency and the color giving rise to the term splenization. Hypostatic congestion occurs in exhausting febrile conditions, especially in typhoid fever, in heart disease, in cachectic states, in late stages of chronic diseases, and with especial frequency in old people who for any cause are long bed-ridden.

Cyanosis and dyspnea of varying grade are the usual symptoms. Cough and sputum, often blood streaked, are frequently present. The percussion note at the bases is dull. The breath sounds are diminished in intensity or distant and blowing in quality, the voice sounds intensified and bronchial in quality. Numerous moist râles usually accompany inspiration. If the condition to which the hypostatic congestion is secondary is amenable to treatment or is recovered from, the edema and congestion rapidly subside and the collapsed lung is redistended. If, on the other hand, the hypostatic congestion persists for a long time, infection occurs and bronchopneumonic areas of inflammation develop, a condition spoken of as hypostatic pneumonia. This is a frequent cause of death in long standing cardiac disease and in all chronic diseases. The advent of infection is often difficult to appreciate. Fever is the safest guide, although it is seldom high and sometimes is absent. Patches of consolidation may be outlined over the lower lobes. Cyanosis, dyspnea and cough may become aggravated. Hypostatic bronchopneumonia is usually quickly fatal.

Treatment.—In hypostatic congestion the circulatory conditions must be carefully watched and when there is need supported by appropriate remedies. In all protracted illness, especially when the patient is comatose or somnolent, regular and frequent change of posture should be ordered. This is particularly important in old people after operation, and they should be gotten into a sitting posture and out of bed as soon as conditions will permit. When pneumonia develops, in addition to heart stimulants, sedatives and expectorants may be used.

EDEMA OF THE LUNGS

In long standing passive congestion of the lungs and in hypostatic congestion serum exudes from the distended capillaries into the interstitial tissue and into the alveoli and bronchioles. The exudate may vary from a little moisture in the alveoli to amounts of serum yielding a half liter of thin serous sputum in twenty-four hours. Symptoms vary with the amount of exudate. When slight they are those of passive congestion with a small or larger number of moist râles at the bases; if larger in amount there is cough and profuse expectoration with râles more abundant and heard over a wider area, and often dullness and diminished breath sounds at the bases. The degree of edema varies from day to day with changes in the underlying circulatory condition. Unless the edema clears up with improvement in the circulation, bronchopneumonia usually develops as a terminal infection.

In contrast to this chronic form of pulmonary edema there is an acute form with more dramatic symptoms which is associated with a variety of disease conditions. Patients with heart or kidney disease, and rarely persons apparently in good health, are suddenly seized with violent dyspnea. They gasp for breath, bloody froth exuding from the mouth and nose, and fall over dead. Or they may become unconscious and breathe heavily for an hour or two, the heart action gradually coming to a stop. At autopsy disease of the heart or kidneys is usually discovered, but occasionally no concrete anatomical abnormality is found to explain these singular and fatal symptoms.

More commonly the symptoms of pulmonary edema come on less startlingly but still acutely. The patient suddenly becomes very short of breath, develops an harrassing cough and expectorates a large amount of serous sputum. The dyspnea grows more intense, there is pain and oppression over the chest, the skin becomes blanched and there is extreme anxiety. Tracheal râles become louder and louder, and moist ronchi so obscure all other sounds over the chest that the breath sounds and heart sounds can not be appreciated. The extremities become cold, the skin is livid and bathed with sweat, the patient becomes unconscious and death soon closes the scene. At any stage of these events improvement may begin and the distressing symptoms slowly disappear. The attacks usually last from two to four hours and have a tendency to recur. One patient is reported to have had seventy-two such attacks in less than three years.

Attacks of acute pulmonary edema are usually associated with disease of the heart, with nephritis and with arteriosclerosis. In nephritis it may in some instances be due to an intoxication, but in both nephritis and arteriosclerosis it is more often the result of cardiac involvement. In these cases hypertension is usually present and the attacks of edema may be accompanied by marked rise in the blood pressure.

As a terminal event in infectious diseases and in all chronic illness pulmonary edema frequently supervenes. In such instances the edema is an unimportant event as far as the outcome of the illness is concerned. As Cohnheim aptly put it, the patients do not die of pulmonary edema, they have pulmonary edema because they are dying.

Patients occasionally develop pulmonary edema after the removal of a pleural effusion. The condition is associated with the expectoration of large amounts of albuminous sputum. It is particularly apt to follow the aspiration of effusions of long standing. While the mechanism of the edema is not clearly understood, in many instances it seems to be due to suction upon a lung which is unable to expand on account of pleural adhesions.

In acute pulmonary infections edema may occur and the inflammation then subside without a definite pneumonia developing. In severe infections pulmonary edema may be extreme and the patient die before consolidation occurs.

The pathogenesis of pulmonary edema has given rise to much discussion, and a number of explanations have been offered, none of which fits all cases. No doubt congestion is the most important factor, and this element is usually present. Increased permeability of the blood vessel walls is assumed to occur. Inflammatory and toxic influences are important factors, especially in the presence of passive congestion. A nervous type of edema is also described, supported by experiments demonstrating that pulmonary edema occurs readily in animals with the vagi cut. Apparently too much emphasis has been put upon the serious effects of edema itself. A statement in common use is that patients drown in their own serous effusion. Winternitz has shown that the presence of fluid in the lungs does not cause important symptoms, and edema is a serious symptom not because it is fatal or harmful in itself, but because it is an expression of a serious derangement of function which is frequently fatal.

Treatment.—Since myocardial insufficiency is the usual cause of pulmonary edema the treatment of the condition is essentially the treatment of cardiac failure. Bleeding is often of value in acute pulmonary edema, especially when associated with mitral valve disease or hypertension. Atropin is widely recommended but is of doubtful benefit. Artificial respiration has been used; there is some experimental evidence to recommend it. In patients with hypertension vasodilators are sometimes beneficial. They should be used only when hypertension is present and their effect controlled with the sphygmomanometer. There has been much discussion about the use of morphia, but it is my conviction that it does no harm and in the acute cases I regard it as indispensable.

Embolism, Thrombosis and Infarction

Emboli that reach the lung are nearly always bits from thrombi lodged in the right side of the heart or in the systemic veins. Other types of embolism occur, but are of relatively little importance, excepting fat embolism and air embolism. Fat embolism occurs chiefly after extensive injury to the bones; it occurs rarely in disease or injury to fatty tissue elsewhere, in diabetes and phosphorus poisoning. The condition can seldom be diagnosed clinically, but may be suspected if cyanosis and dyspnea follow immediately upon injury to the bones. It may play a part in the production of the symptoms of shock following such an injury. Air embolism may follow the opening of large value. Under such circumstances, the pulmonary embolism plays no part in the production of the serious symptoms that sometimes follow. These symptoms are due to dilatation of the right ventricle.

Pulmonary emboli are particularly common in heart disease associated with distension of the right side of the heart. At autopsy mural thrombi are found in the auricular appendage or lodged amongst the papillary muscles. They occur with special frequency in mitral stenosis, but are not uncommon in every form of myocardial insufficiency. Pulmonary embolism may follow the development of a thrombus in the right ventricle at the site of a coronary infarct. I have seen one remarkable instance follow shortly after a severe attack of angina.

Thrombosis in the systemic veins is frequently followed by pulmonary embolism. Almost invariably from this source come the large emboli that cause grave symptoms and sudden death. Often the venous thrombosis is unsuspected until pulmonary embolism occurs. The causes of venous thrombosis cannot be discussed here. They are varied and many of them obscure. Venous thrombosis occurs frequently with all infectious diseases, although much more commonly with some than with others. It often follows operation, even when infection is absent. After childbirth there is extensive thrombosis of the uterine venous sinuses, and the pelvic veins often become thrombosed, even when there is no evidence of infection. Sometimes phlebitis and venous thrombosis occur independently of any other apparent disease. Stasis in the venous circulation is often associated with thrombosis, sometimes with, sometimes without added infection. Certain diseases of the blood predispose to clotting and are often accompanied by venous thrombosis, for instance chlorosis. In all of these conditions pulmonary embolism may occur, but clinically it is observed particularly in connection with disease of the heart, after infectious diseases, and after operation and childbirth.

Pulmonary embolism may occur almost simultaneously with the formation of the venous thrombus, the whole thrombus or parts of the thrombus becoming detached and being carried to the lungs. If we assume that venous thrombosis occurs at the time of operation, then from the fifth to the twelfth day after the formation of the thrombus is the usual time for embolism to occur. This same time relation apparently exists in venous thrombosis due to infectious diseases. Embolism may occur during the third week following operation, or after childbirth, and these late emboli are often large. Emboli go much more frequently to the lower than to the upper lobes, and more frequently to the right than to the left lower lobe.

When a branch of the pulmonary artery is occluded, an infarct is often produced. The pulmonary arteries are terminal arteries, but there is a free anastomosis between the capillaries of the different branches, and the bronchial artery nourishes the bronchi and the adjacent pulmonary tissue. This free anastomosis is sufficient to prevent the occurrence of infarction in normal lungs, even when large branches of the pulmonary artery are occluded. Virchow in his classical experiments succeeded in producing pulmonary infarcts only when he introduced infected material into the pulmonary artery. For the occurrence of pulmonary infarction there must be some circulatory disturbance in the lung or some injury to the lung tissue in addition to embolism. This combination of circumstances is found particularly in the presence of passive congestion.

Pulmonary infarcts produce firm, dark red masses in the lungs of a triangular or pyramidal form. They are dry and often remarkably hard, and since the base usually reaches the pleural surface, they are elevated and easily discernible. The pleural surface over the infarct is roughened. At the apex of the infarct the embolus can usually be seen lying in the pulmonary artery. Microscopically the alveoli and all of the tissue in the involved area are packed with blood. When the infarct heals it is replaced by dense scar tissue. It seems likely from clinical observation that some infarcts are absorbed with functional restitution of the involved area. If the infarct becomes infected abscess and gangrene may occur. The proximity to the pleural surface may lead to empyema and pneumothorax.

The *symptoms of pulmonary embolism* depend upon the size of the artery that is occluded. If the embolism occludes the trunk of the pulmonary artery, or both main branches, death occurs almost instantly. Occlusion of both the right and left pulmonary artery is usually produced by a large embolus straddling the bifurcation and projecting into both vessels. A patient convalescing from an infectious disease or from childbirth sits up in bed or gets up for the first time and suddenly falls over pale and unconscious and after a few gasps is dead. Or the patient is suddenly seized with extreme dyspnea, struggles for breath, becomes pale or cyanotic, may call for help or say a few words, becomes unconscious, and pulse and respiration rapidly fail. When a large embolus passes the bifurcation it lodges usually in the right main branch of the pulmonary artery. Death may occur as promptly as when the pulmonary trunk is plugged. More often the symptoms are prolonged for an hour or more. The patient suddenly becomes extremely dyspneic and presents the clinical picture of profound shock. The pulse is rapid and small, the skin pale or cyanotic and cold, bathed in sweat, the features portray mortal anxiety. The patient continues to struggle for breath, as the pulse grows weaker and weaker, and finally becomes unconscious with a rapidly failing circulation. Recovery is said to have followed occlusion of one of the main branches of the pulmonary artery, but since the decision rests upon clinical evidence there is doubt about the accuracy of the interpretation.

The symptoms following occlusion of one of the main branches of the pulmonary artery cannot be satisfactorily explained on a mechanical basis alone. When the main trunk of the pulmonary artery is obstructed no blood reaches the left ventricle and cerebral anemia is at once produced. But one might anticipate that the heart could contend successfully with one half of the pulmonary arterial bed cut off. That the cardiac efficiency plays an important part in the duration of the symptoms there can be no doubt, and patients who do not die at once die gradually of circulatory failure. What part vasomotor phenomena and what part myocardial insufficiency play in this failure is not clearly established. It seems altogether likely that the sudden occlusion of one of the main branches of the pulmonary artery produces profound reflex, as well as direct mechanical, disturbances.

When the embolus passes the main branch of the pulmonary artery and lodges in one of the large subdivisions a different train of clinical symptoms is evoked. With the lodging of the embolus there is suddenly severe pain, followed at once by a rapid rise in the pulse rate, cyanosis and dyspnea. These symptoms gradually subside but are usually followed in from twenty-four to forty-eight hours by the symptoms of pulmonary infarction. In patients in weakened condition, especially in those with myocardial disease, such emboli may be followed by rapidly fatal cardiac failure. With the development of a pulmonary infarct there is usually pain in the side, cough and bloody sputum. The temperature rises and there is dullness, diminished or blowing breath sounds and fine moist râles usually over the right lower lobe. This group of symptoms often leads to the diagnosis of pneumonia. The fever usually lasts from eight to ten days falling gradually to normal. At times the temperature-pulse relation is so characteristic that a glance at the bedside chart is sufficient to make the diagnosis. After operation let us say the temperature and pulse rate are normal. Suddenly the patient has a sharp pain in the chest and the pulse-curve rises abruptly from eighty to one hundred and forty. The temperature curve remains at the normal level, but at the end of from twenty-four to forty-eight hours the temperature gradually rises as the pulse-curve slowly falls. Temperature and pulse then both remain high for six or eight days and then both gradually fall again to normal. The sputum of infarction is quite characteristic although the same type of sputum occurs in other conditions. It is a bloody sputum dark in color and diffusely and evenly colored. Frequently more or less fluid blood is mingled with the masses of bloody sputum.

When the embolus plugs a small branch of the pulmonary artery only slight symptoms are produced. If no infarct forms the accident passes unnoticed. If a small infarct forms there is pain in the side lasting for a few hours or a few days, bloody sputum and usually a little fever. Bloody sputum occurs in from eight to twenty-four hours after the infarction. If numerous small infarcts occur at the same time or nearly simultaneously, symptoms are produced similar to those caused by occlusion of a large vessel. However, such an occurrence is exceedingly rare. Small infarcts usually give no physical signs, at most showers of fine crisp pleural râles are heard over the area of pain. Larger infarcts may give a little dullness and slight changes in the character of the breath sounds.

When infected emboli reach the lung they produce in addition to the mechanical changes the usual results of infection. The emboli are often multiple and give the characteristic clinical picture of septic pneumonia encountered so typically in postpartum streptococcus infections. If the infarct be single an abscess may form. Empyema and gangrene are less common. Pulmonary emboli occur commonly in streptococcus viridans' endocarditis, the emboli coming from vegetations in the right heart or from mural thrombi as in non-bacterial valvular heart disease or from thrombi in the peripheral veins. Even though the streptococcus viridans be present in the emboli suppuration does not occur and the infarcts progress as do bland infarctions. Pleural effusion usually of slight or moderate extent commonly follows pulmonary infarction even though the emboli be uninfected.

The *diagnosis of pulmonary embolism* is not difficult if the possibility be held in mind. I am convinced that it occurs far more frequently than is usually stated. In my experience nearly all postoperative pleurisies and most postoperative pneumonias (so-called) are really the effects of pulmonary embolism. During convalescence from infectious diseases sudden death, the abrupt onset of circulatory symptoms or collapse are far more commonly due to pulmonary embolism than to primary cardiac failure, although they are usually ascribed to the latter cause. There are a few important points in this connection which should be emphasized. (1) Venous thrombosis is extremely common after all operations, especially after abdominal and pelvic operations, even though the operation be "clean" and convalescence uneventful. These thrombi usually pass unrecognized unless pulmonary embolism occurs. (2) Venous thrombosis occurs commonly in infectious diseases, particularly in pneumonia and typhoid fever. It often passes unrecognized clinically. (3) Venous thrombosis is the commonest cause of a little "unexplained" fever persisting through convalescence from operation or an infectious disease. (4) Extensive pulmonary embolism and infarction may occur without the patient having bloody sputum or indeed any sputum. (5) In patients convalescing from operation or infection, sudden pain in the chest, associated with simultaneous acceleration of the pulse rate, and a little later by fever and the physical signs of pleurisy, consolidation or pleural effusion practically always means pulmonary embolism. Characteristic bloody sputum when it occurs certifies the diagnosis. (6) Small pulmonary emboli frequently precede larger fatal emboli. An appreciation of these warning symptoms may sometimes prevent graver accidents.

Little need be said about the *treatment of pulmonary embolism*. Where the occurrence should be feared, extraordinary care must be exercised to enforce rest, as nearly as possible absolute. For collapse when it occurs the usually employed stimulants are indicated. If the patient survives, the ensuing circulatory symptoms must be met with appropriate remedies. Morphia is indispensable. Small infarcts need no special treatment. Pleural effusion is seldom sufficiently large to require aspiration. If it seems wise to withdraw some of the fluid, aspiration should be performed cautiously and conservatively.

Pulmonary thrombosis is extremely rare except in association with embolism. As an independent condition it occurs occasionally in children during severe infections. The clinical picture is usually that of bronchopneumonia. Thrombosis of small branches of the pulmonary artery occurs sometimes in infectious diseases and in intoxications. They have no important clinical significance aside from the underlying condition that causes them.

HEMOPTYSIS

Hemoptysis signifies bleeding from the lungs or bronchi. Even blood streaked sputum may be included under this term although it has come to be used generally in a more restricted sense to signify the expectoration of blood. Used in this sense it is equivalent to frank hemoptysis and does not embrace blood streaked or bloody sputum. It is important to define what the term includes, because while all conditions which cause blood spitting commonly cause also the expectoration of bloody sputum, there are many conditions which are almost regularly associated with bloody sputum and yet rarely cause hemoptysis. Pneumonia, both lobar and lobular, and chronic passive congestion of the lungs are amongst the commonest causes of bloody sputum but they seldom cause blood spitting. The exceptions are chiefly certain cases of bronchopneumonia complicating virulent specific infections, particularly influenza. Lobar pneumonia is very rarely ushered in with hemoptysis. The common causes of blood spitting are pulmonary tuberculosis and pulmonary infarction; less common causes are bronchiectasis, growths, abscess and gangrene; uncommon causes are trauma, aortic aneurysm, syphilis, constitutional diseases as purpura hemorrhagica, hemophilia and scurvy, animal parasites particularly echinococcus and pulmonary distoma, leprosy, aspergillosis, actinomycosis, streptothricosis, etc. The presence of blood in the sputum is always an important symptom from the diagnostic standpoint. It is seldom in itself of great clinical importance. Large, fatal pulmonary hemorrhage is uncommon and occurs only when the aorta or a large branch of the pulmonary artery is eroded or ruptured. The former condition is almost always due to aneurysm, the latter to pulmonary tuberculosis or malignant disease. Fatal hemorrhage in tuberculosis is usually from rupture of an aneurysm of a branch of the pulmonary artery formed in a lung cavity.

The *diagnosis of hemoptysis* is sometimes difficult. It must be distinguished from bleeding from the upper respiratory passages and from hematemesis. If there is doubt the history is usually conclusive. In hemorrhage from the lung after the first hemoptysis is over the patient continues during the following twenty-four to forty-eight hours to cough up dark clots of blood. Bleeding from the posterior nares may simulate hemoptysis, but inspection at the time of bleeding or a careful inquiry about the symptoms will nearly always distinguish the two. Profuse hemoptysis may be mistaken for hematemesis. I have on several occasions seen a diagnosis of ulcer of the stomach made on the basis of profuse bleeding when subsequent observation showed the patient to have pulmonary tuberculosis. Curiously enough I have never seen hematemesis mistaken for hemoptysis, but no doubt the error does occur.

In most cases hemoptysis needs no special *treatment* as the bleeding is seldom marked. In tuberculosis the great danger is not from the loss of blood, but the extension of the tuberculosis. Careful nursing is more important than the use of drugs. When the bleeding is long continued or frequently repeated, artificial pneumothorax will control it more promptly and more certainly than any other measure. Before inducing pneumothorax, the physician must determine definitely from which side the hemorrhage is coming. This is often impossible. Unfortunately pleural adhesions may prevent pulmonary collapse. Morphia is valuable to allay fear and to quiet an irritative unproductive cough. In pulmonary tuberculosis it must not be used indiscreetly, since by checking cough completely the aspiration of infected blood is facilitated and spread of the disease made more likely. It is impossible to discuss in detail all of the methods that have been used to control pulmonary bleeding. Some of the methods are harmful, most of them without value. The nitrites, pituitary extract, atropin, calcium and the injection of serum are still frequently employed.

DISEASES DUE TO ALTERATION OF THE ALVEOLAR LUMEN

EMPHYSEMA

The term emphysema is used to designate a number of different conditions which are distinguished by prefixing adjectives. It is convenient to divide these conditions into two groups; on the one hand ordinary, genuine, or true emphysema, also described as substantive, hypertrophic, idiopathic and diffuse vesicular emphysema, on the other hand acute vesicular, compensatory, senile and interstitial emphysema. It would be a great advantage to restrict the term emphysema to the first-named condition. Acute vesicular and compensatory emphysema are better termed pulmonary distension. In both the pulmonary distension is due to increased intra-alveolar pressure and not to structural change in the lungs. If the pressure is released the lungs return to their normal condition. If the increased pressure is maintained for a long time atrophy of the alveolar walls occurs, the lung loses its resiliency and a condition in all respects similar to true emphysema occurs. Pulmonary distension occurs in its most typical and extreme form in severe bronchial asthma. It occurs also in any other condition interfering with the easy escape of air from the lungs, as in laryngeal stenosis, diffuse bronchitis, pertussis, etc. Compensatory emphysema is a local distension of one portion of the lungs due to disease obliterating another portion. It occurs about atelectatic, inflamed, contracted or consolidated portions of the lung, in the opposite lung when one is compressed or obliterated by disease. Senile emphysema is a part of the atrophic change that occurs everywhere in the body with advancing years. The alveolar walls become atrophic and the lungs lose their elasticity. In contrast to true emphysema the lungs are small and retracted. Interstitial emphysema has no connection with the other conditions included under emphysema. Following rupture of the alveolar walls, air enters the interstitial tissue of the lung, reaches the mediastinum and may extend to the subcutaneous tissues of the neck and trunk.

Pathology

In long-standing emphysema the chest assumes the characteristic form designated "barrel shape"; the chest is increased in all diameters, especially in the anteroposterior, the ribs are wide apart, the costal angle is broad and the costal margins flare. On opening the chest the lungs fail to collapse and the diaphragm is low. The surface of the lungs is pale, and often at the apex or base and along the margins vesicles are seen, varying in size from small blebs to bullae as large as an orange. Although the lung is greatly distended, it feels soft and light and the finger indentations often persist. Normal crepitation is replaced by the sensation of squeezing large bubbles. Microscopically the alveolar walls are found to be thin and in many places broken through, large air spaces being formed by the rupture of a number of alveoli. Broken shreds of elastic tissue may be demonstrated by special stains. The capillaries are constricted and many of them obliterated.

In the production of emphysema two factors must be considered, mechanical factors which increase the intrapulmonary tension and cause distension, and nutritive factors that decrease the resistance of the alveolar wall. Pulmonary distension is the essential factor, but no doubt the nutritive factor is also important, because apparently there is a great individual difference in the ease with which mechanical factors produce emphysema. No doubt distension itself, by interfering with the blood flow in the capillaries, is an important factor in disturbing the nutrition of the alveolar tissue; infection may play a part; and it is altogether likely that the quality of the elastic tissue may vary in different persons. Some clinicians have emphasized a family tendency to emphysema. Others have claimed that the elastic fibers in emphysematous lungs are less numerous than in normal lungs, but the careful study of Tendeloo contradicts this contention.

A very extensive literature is devoted to experiments and discussions concerning the exact way in which mechanical factors produce pulmonary distension. Freund would explain it all by changes in the costal cartilages leading to enlargement and rigidity of the thorax. Hofbauer and others emphasize the importance of inspiratory distension. The majority of observers put chief emphasis upon obstruction to expiration. Clinical observation, it seems to me, strongly supports the predominant part played by expiratory obstruction. The conditions most often causing emphysema are bronchitis and asthma. In a severe attack of asthma, pulmonary distension is extreme, and simply to look at an asthmatic patient breathing shows clearly enough how the pulmonary distension comes about. Violent inspiratory efforts forcibly distend the lung and then follows the slow, labored, wheezing expiration which is unsuccessful in its attempt to express the air completely before the next inspiratory effort begins. This same mechanism, though not so extreme, occurs in bronchitis involving the small bronchi, and also under the conditions which cause local emphysema. Whether emphysema can occur solely with violent inspiratory efforts when there is no expiratory obstruction may be questioned. When emphysema is marked the blood flow in the lungs is seriously impaired, the pressure in the pulmonary circulation rises and the right side of the heart hypertrophies. Later the right ventricle dilates and the heart condition then plays an important part in the production of the symptoms commonly associated with emphysema.

Symptoms

The cardinal symptoms of emphysema are dyspnea, cyanosis and cough. Dyspnea is usually the first symptom and the most constant. In the early stages it may be but slight even on exertion, but if the disease progresses it becomes more and more marked until in some instances it is extreme even when the patient is at rest. The degree of bronchitis that is present has much to do with the intensity of the dyspnea. In late stages myocardial insufficiency also plays an important role. The cardiac condition probably explains the severe paroxysms of dyspnea which are not uncommon in advanced emphysema. Cyanosis is nearly always present and may be extreme. Osler comments upon the fact that emphysema is the only condition, besides congenital heart disease and poisoning with certain anilin derivatives, in which patients walk about in apparent comfort with a startling degree of cyanosis. Some cough is nearly always present and varies from time to time with the degree of bronchitis. Sputum may be absent or it may be profuse and mucopurulent. The amount and the character of the sputum also vary with the bronchitis.

The symptoms of emphysema therefore depend in large part upon the associated bronchitis and the condition of the heart. It is not uncommon to see patients who for many years pass with comfort through the summer months and become dyspneic, blue and wheezy each winter with the onset of bronchitis. The effects of emphysema upon the right side of the heart are the same as hypertension exerts upon the left side, and a similar chain of symptoms ensues. The right ventricle becomes hypertrophied, then dilates and finally fails. In terminal stages the symptoms of myocardial insufficiency may predominate and the importance of the pulmonary condition may be overlooked until at autopsy the tremendous enlargement of the right side of the heart demonstrates the true course of events. This oversight occurs frequently in hospital practice where patients are so often seen in the very last stages of their illness.

The clinical course of emphysema varies with the underlying condition, the degree of bronchitis and the cardiac efficiency. Many cases last an indefinite number of years and the condition remains practically stationary. They have a little dyspnea on exertion, but are otherwise comfortable until they contract bronchitis, when more marked symptoms come on, to subside again as the bronchitis clears. In other instances the disease runs a more rapid and uniformly progressive course. A bronchial infection fails to clear up, cough and expectoration persist, dyspnea and cyanosis become more and more marked, and bronchopneumonia or cardiac failure terminates the course of events. In such instances diffuse bronchiectasis is usually associated with the emphysema. In certain cases of pulmonary infection, especially tuberculosis, a diffuse pulmonary fibrosis often causes marked and occasionally extreme emphysema. The distended lung masks the physical signs of the tuberculous disease and the underlying condition is unsuspected. Repeated and careful sputum examinations not infrequently demonstrate tubercle bacilli in the cases of chronic bronchitis and emphysema that frequent the out-patient department of hospitals during the winter months. In asthma, recurring and long continued pulmonary distension is often followed by structural changes in the lung leading to true emphysema. The lungs then remain permanently distended, and dyspnea, cough, sputum and wheezing vary with the intensity of the bronchitis and the degree of bronchial spasm. Unless some intercurrent disease carries them off the patients die of bronchopneumonia or cardiac failure. A congenital form of hypertrophy of the lungs is described. In this condition the lungs are abnormally large, but they show no pathological change and do not produce the usual symptoms of emphysema.

Physical Signs

The physical signs of emphysema are very characteristic. The chest is full and rounded, the anteroposterior diameter much increased and often equal to the transverse. The interspaces are wide apart, the costal angle is wide and the costal margins stand out prominently. The clavicles are prominent, and the neck appears short from the elevation of the thorax and thick from the hypertrophied respiratory muscles. The veins in the neck are full and easily visible. As a rule no pulsation is seen over the heart. In some instances the dilatation of the thorax occurs only in the upper portion, while the lower part remains relatively constricted. Some authors would restrict the term barrel-shaped chest to this type. Both inspiration and expiration are marked by active participation of the accessory muscles of respiration, but although inspiratory efforts may be labored the chest expands but little, the whole thorax being lifted up as a rigid box. The expiratory effort is usually much prolonged and when bronchitis is present accompanied by wheezing. On palpation fremitus is present but diminished; the cardiac impulse is not felt. The percussion note is altered. Usually it is full and deep, and has a drum-like quality that is spoken of as hyperresonance. The resistance felt by the pleximeter finger is often striking. The outline of pulmonary resonance is greatly increased. The apical resonance zones are large, the area of cardiac flatness is obliterated, the lower border of pulmonary resonance extends an interspace or more lower than normal and the border moves little with inspiration and expiration. The breath sounds have a characteristic quality difficult to describe. They are distant and faint, and instead of being normally crisp and vesicular, they are smooth and blowing in quality with somewhat prolonged expiration. Moist and sonorous and sibilant râles are usually present. They vary with the extent of the bronchitis. The heart sounds are distant and faint, and if many râles are present may be inaudible.

The roentgenogram of an emphysematous chest shows the elevated horizontal ribs with intercostal spaces. The chest seems abnormally long on account of the low position of the diaphragm. The heart is usually pulled into a vertical position. The lung fields are strikingly clear; the hilus shadows wide and deep and the bronchial tree shadows unusually well marked.

Frequently the clear pulmonary fields are marked by shadows cast by old inflammatory lesions. These are more common in the upper lobes than elsewhere and probably in most instances represent old tuberculous foci.

Treatment

It is impossible to exercise any direct therapeutic effect upon the emphysematous lung; treatment can only be protective and symptomatic. The one exception is rare cases in young people in which the emphysema seems to be due primarily to abnormal rigidity of the chest wall. Freund has written extensively upon the subject, and a number of cases have been reported by van den Velden and others, in which section of the costal cartilages has given prompt and marked relief.

The main indications for treatment in emphysema are the presence of bronchitis and of myocardial insufficiency. The treatment of these conditions will be found under their proper heading and need not be repeated.

Various devices have been used to relieve dyspnea. Waldenburg's apparatus allows the patient to inspire normal air but expiration takes place in rarified air. In Bruns' apparatus the patient breathes a rarified air on both inspiration and expiration. Kuhn's mask produces diminished pressure during inspiration, normal pressure during expiration. Although the principle of the apparatus varies, and Kuhn's mask might be supposed to increase pulmonary distension, still they all seem to benefit some patients. No doubt the good effect depends chiefly upon their influence on the pulmonary circulation. Rossbach, Hofbauer and others have devised instruments to assist expiratory efforts. They are said to give definite relief. Various breathing exercises are also of value.

A patient with emphysema must be sedulously guarded against deleterious influences. Underlying conditions, especially asthma and bronchitis, must if possible be remedied and recurrence prevented. Eradication of infections in the nose and throat, especially in the paranasal sinuses, change of climate, protection from exposure to weather and dust are important.

ATELECTASIS

When for any reason air is prevented from entering a portion of the lung the imprisoned air is absorbed and the alveoli collapse. This condition of the lung is analogous to its fetal state before dilatation of the alveoli has occurred. Atelectasis is particularly frequent in infants, probably because the lungs are relatively more voluminous than in adults. In adults even after forced expiration the lungs still contain a large amount of residual air, but in infants pulmonary distension is about proportionate to the amount of inspired air. Atelectasis is caused by (1) complete obstruction of the bronchus, (2) compression of the lung and (3) interference with the respiratory movements of the chest.

Massive atelectasis occurs when a large bronchus is completely closed. If the closure is incomplete emphysema and bronchiectasis result. The commonest cause of such obstruction is the presence of a foreign body or pressure from a tumor. Smaller bronchi are frequently occluded by inflammatory exudate. Areas of atelectasis are very common about bronchopneumonic foci. These effects of bronchial obstruction are facilitated by weak respiratory efforts and atelectasis is therefore found particularly in infants and in debilitated adults.

Compression of the lung causes atelectasis by preventing expansion. It occurs in a host of abnormal conditions, pleural effusion, pneumothorax, tumor, enlarged heart, pericardial effusion, increased intra-abdominal pressure, etc.

The most characteristic type of atelectasis due to insufficient respiratory movements is the atelectasis of the new-born. Weak, premature infants are often unable to exert sufficient force to dilate the lungs, but sometimes bronchial occlusion due to aspiration of amniotic fluid, meconium or mucus plays an important part in producing the atelectasis. Cerebral accidents during birth are often the cause of insufficient respiratory movements. In adults the role of the respiratory movements is sufficiently emphasized by the almost exclusive occurrence of atelectasis in debilitated subjects. In healthy adults who breathe shallowly small areas of atelectasis frequently occur along the borders of the lungs. A single full breath fills out the collapsed areas. The remarkable massive pulmonary collapse (see Volume II, Chapter IV) that sometimes follows wounds to the chest is probably due to temporary paralysis of the muscles of respiration.

The atelectatic portion of the lung is contracted and of a deep blue or purplish color. It feels soft and pasty and does not crepitate when passed between the fingers. On section it is dry, inelastic and not granular. If the collapse lasts a long time the alveolar walls adhere together and dense fibrous tissue indurates the lung so that it cannot again expand. This condition frequently occurs after artificial pneumothorax.

Symptoms

In congenital atelectasis the infants are asphyxiated at birth. If they are resuscitated by artificial respiration, they may live for days or weeks. They are usually feeble and breathing is shallow and rapid. The physical signs are those of pneumonia. Vigorous infants may recover completely, but a number of those who live retain atelectatic areas and subsequently may develop bronchiectasis.

Acquired atelectasis usually adds no important symptoms to the condition with which it is associated. Its presence favors the development of bronchopneumonia. There is dullness, diminished or blowing breath sounds and often fine crisp râles over the collapsed areas.

Abrams has pointed out that small areas of atelectasis frequently occur in healthy adults. They are situated along the margins of the lungs especially at the ends of the clavicles, in the supraspinous fossa and about the angle of the scapula. They give a little dullness on percussion and deep inspiration is accompanied by fine crisp râles. The signs disappear after one or two deep breaths. The condition is important only as a possible source of error in diagnosis.

Krönig has described collapse "induration" of the right apex which he believes is commonly diagnosed pulmonary tuberculosis. The apical resonance zone is contracted, there is diminished mobility, the breath sounds are harsh and often blowing and fine râles may be heard. The condition, which I believe to be very uncommon, is said to be associated chiefly with nasal obstruction. In contrast to pulmonary tuberculosis there are no constitutional symptoms and the movements of the lower borders of the lungs are normal.

Of particular interest is the massive pulmonary collapse that sometimes follows wounds to the chest (see Volume II, Chapter IV). It occurs seldom in civil practice but was encountered frequently during the war, and until the condition was understood gave rise to grave errors in diagnosis. It often follows non-penetrating and apparently slight wounds to the chest wall and frequently occurs on the side opposite to the one wounded. The physical signs simulate pleural effusion or pulmonary consolidation. It is distinguished from pleural effusion by the retraction of the side, the high position of the diaphragm and the marked displacement of the heart towards the affected side; from pneumonia by these same physical signs and the absence of the usual symptoms of pneumonia. Not infrequently massive collapse occurs in association with a small hemothorax, and under such circumstances the diagnosis is especially difficult.

Treatment

In the congenital form artificial respiration is often life saving. For the acquired form there is no special treatment aside from the treatment of the underlying condition. In debilitated patients change of posture, hydrotherapy and other measures that stimulate respiration should be used. The treatment of associated bronchitis and measures that facilitate expectoration are important.

Diseases due to Foreign Bodies

Pneumonoconiosis

Pneumonoconiosis is the term introduced by Zenker to designate the changes that occur in the lungs due to the inhalation of dust. These changes depend partly upon the quantity of dust that is inhaled, but more particularly upon the physical and chemical properties of the dust. The first important division of dusts is into organic and inorganic dust.

Organic dust is often inhaled in large quantities in the textile trades, the dust coming from cotton, silk, wool, flax, hemp, hair, etc. Even under conditions of extreme dustiness these organic particles cause no mechanical changes in the lungs. Landis, for instance, in a study of a particularly dusty carpet manufactory was unable to discover any pulmonary changes in the workmen differing from those found in most urban dwellers. Dust from tobacco leaves has long been held to be very injurious mainly because tuberculosis is common among tobacco workers. However, there is very little tobacco dust in tobacco manufactories and what little there is causes *per se* no appreciable effect upon the lungs. The prevalence of tuberculosis must be ascribed to other causes. Organic dust may be injurious (1) by carrying with it into the lungs particles of inorganic dust, or (2) bacteria and (3) by evoking certain complex biological responses to the specific protein in the dust. The first two possibilities will be referred to later. It is often noticed amongst workers exposed to organic dust that the new hands develop fever, cough, rhinitis and headache, while the older employees breathe the dust with impunity. Sometimes definite asthmatic symptoms develop. The condition is often referred to as "shoddy fever" and "mill fever". A similar group of symptoms occurs in grain threshers. These symptoms represent a hypersensitive or anaphylactic reaction to the inhaled protein and are analogous to the manifestations of hay or pollen fever.

Inorganic dusts may be divided into two groups with reference to their effects upon the lungs (1) those that cause but little change in the lungs, (2) those that cause marked change in the lungs. To the first group belong coal, soot, shale, slate, clay, limestone, plaster of Paris and cement; to the second group silica, quartz, flint, emery, carborundum, sandstone. The least dangerous of dusts are soot and coal, the most dangerous is silica. The facility with which dust produces changes in the lungs depends upon (1) its chemical composition, (2) its physical properties, (3) the condition of the lungs and the vital reaction to the deposited dust particles. Collis has emphasized that the harmfulness of dusts varies in proportion to the dissimilarity of their composition to the elements of which the body is normally composed. Thus lime dust in spite of its fine angular particles is relatively innocuous. No doubt the physical properties of dust are still more important factors. The finer, the harder, the more angular the dust particles the more potent are they to produce marked pulmonary changes. Silica and particles of iron and steel have these properties to a marked degree. Silica is far more important than iron and steel as a cause of fibrosis because it is one of the commonest dusts to which workmen are exposed, whereas exposure to fine particles of iron or steel is extremely uncommon. The size of the dust particles is important because only very fine particles float about in the air and are inhaled directly into the alveoli and, what is equally important, only fine particles can be taken up by phagocytes and disseminated through the lung tissues. McCrae and others have made careful measurements of the siliceous particles in lungs and find that the average diameter is below 2.5 microns and that practically none exceeds twelve microns. Particles below one micron are invisible by polarized light and so cannot be measured, but it is likely that these minutest particles make up the larger part of the silica deposited in the lungs. It has been estimated in the gold mines of South Africa that immediately after blasting, one cubic meter of air may contain as much as 500 mg. of siliceous dust and that in this volume there may be 86,000,000,000 particles of a diameter of twelve microns or less. Although the particles of dust from plaster of Paris have sharp angles, they produce no changes in the lungs, no doubt on account of their relative softness and the ease with which they diffuse in water.

The importance of the vital reaction of the lung in determining the development of fibrosis is plainly seen in the relative "resistance" of different men working under the same conditions. Apparently some develop fibrosis and suffer from symptoms more easily than others. Most of the dust that is inhaled is deposited upon the bronchial mucous membrane and mechanically swept out of the lung by the ciliated epithelium. However, it is altogether likely that some fine dust particles are swept directly into the alveoli with the inspired air. Much of the dust that reaches the alveoli is carried out again in the expired air or by coughing, and in the flow of secretion to the bronchial tubes. However, some particles are deposited and no doubt their smallness and angularity determine largely their hold upon the alveolar walls. These particles are taken up by phagocytes and transported, often in relays, to the lymphatics in the interstitial tissue or under the pleura, and through these lymphatics to the bronchial glands. It is suggested that a second mode of eliminating the dust is that phagocytes pierce the alveolar walls and thus deposit the particles in the alveolar spaces from whence they are discharged in the sputum. In silicotic or anthracotic lungs, dust laden phagocytes are found in the alveoli, and the sputum of patients is pigmented months after they have been away from dust. By this method the lungs are kept clear and in the early stages dust particles are found chiefly under the pleura and in the bronchial nodes. Later however, the lymphatics become occluded and the dust particles are deposited along their course and in the interstitial tissue. This process explains the marked pigmentation that occurs about patches of fibrosis. A necessary step in the development of fibrosis, therefore, is the plugging of the lymphatics, and persons with pulmonary lymphatics occluded by previous disease will probably develop fibrosis more readily than those with normal lungs. Mavrogordato's observations on experimental animals led him to suggest that certain dusts are more readily eliminated than others, and that those easily eliminated produce a marked initial reaction in the alveoli with shredding of epithelium. Siliceous dust causes little reaction and tends to accumulate in the lung, while coal and soot are easily gotten rid of. He found further that coal and siliceous dust mixed together produce less change in the lungs than pure siliceous dust. In other words dusts that produce an initial reaction tend to carry out with them the more inert.

Pathological Anatomy

Changes produced in the lungs by dust are uniform, although the degree to which these changes occur varies markedly with the different dusts. More or less pigmentation is found in the lungs of all adults living in cities, but this is not regarded as a pathological condition. From slight fibrosis that does not impair the functional capacity of the lungs to extreme grades of induration every transition is found. Since the most characteristic and most marked changes occur in silicosis this condition is selected as best illustrating the sequence of events. Watkins-Pitchford gives an excellent description of silicotic lungs, and divides the condition into four stages. In the first stage the lungs are edematous and congested, of a bright red color. The connective tissue strands are unusually prominent. Scattered throughout the lungs are islands of black pigmentation, some of which stand out above the general level of the cut surface. The lung is crepitant and floats in water. In the second stage the islands of pigmentation are larger and more numerous and many of them coalesce. The cut surface of the lungs is no longer red, but of a dark gray color, and from the prominence of the pigmented areas it is coarsely granular. There is still slight crepitation and the tissue floats in water. In the third stage the whole surface of the lung is more or less uniformly pigmented, the areas of normal lung tissue being obliterated by the growth of pigment bearing connective tissue. This stage is characterized by the formation of "silicotic nodules". These are very firm circular, oval or polygonal areas of light gray color which gradually replace the pigmented areas seen in the first two stages. They appear as discrete nodules on section, but they are in reality the cut across branches of a ramifying fibrosis. The surface of the lung is now deeply pigmented and studded over with these light gray nodules. The fourth stage is marked by a great increase of the gray fibrotic areas, which coalesce to form a dense, airless tissue. This tissue has no longer any resemblance to the normal lung tissue which it has replaced. On section there is a gray background stippled with black and traces of brown, resembling gray granite. At this stage the lung tissue sinks in water.

While pulmonary fibrosis usually proceeds gradually from one to the other of these four stages, that is from discrete to reticulated pigmentation, and from discrete to diffuse fibrosis, the details of the different stages are not always clearly marked. Occasionally the second or third stage may be omitted. Frequently all four stages are present side by side in the same lung or in a single lobe. The black pigmentation is not due to silica but to the coal and soot inhaled with it, the presence of these admixtures serving admirably to point out the location of the translucent and colorless particles of quartz. When the fourth stage has been reached necrosis of the areas of connective tissue frequently occurs. The central part of the diffusely fibrosed areas soften and then liquefy, and various sized cavities are formed. A secondary tuberculous infection frequently complicates the picture.

On opening the chest of a patient with marked pneumonoconiotic fibrosis the lungs are found distended. This failure to collapse is partly due to the loss of elasticity, but also to dense pleural adhesions. In no other condition excepting perhaps chronic tuberculous pleurisy do such dense adhesions occur. The diaphragm is often distorted by the adhesions, and there may be difficulty in removing the lungs from the chest. The organs are dense and tough and heavy. On section they may creak. In advanced cases of silicosis the organs may weigh three times their normal weight. This increased weight is due in small part to the fibroid tissue, but in greater part to the contained silica, Kussmaul having found that in some instances the ash remaining after incinerating the lung made up from forty to fifty per cent. of the total weight. Cavities are often found in the lung, due usually to an associated tuberculous infection, but they may be due to bronchiectasis, to pyogenic infection or to simple necrosis of the scar tissue.

Microscopical examination of the lungs in the first stage shows the lymph channels and the surrounding tissue filled with dust particles lying free or enclosed in phagocytes. Dust particles are particularly abundant in the collections of lymphoid cells found along the course of the lymphatics. The fibrous tissue about the terminal blood vessels and bronchi shows beginning proliferation. The alveolar epithelium is swollen and many of the cells desquamated. The alveolar walls may be thickened partly by distension of the capillaries, partly by the formation of a young cellular connective tissue. In the second stage there is a larger amount of connective tissue about the blood vessels and bronchioles, and the caliber of these vessels may be diminished. The alveolar walls too are thickened, and the alveoli are filled with desquamated epithelial cells and phagocytes filled with dust. These cells may fill the alveoli and the contents gradually undergo organization. In the third stage numerous alveoli are obliterated by this ingrowth of connective tissue, and the perilobular bands of connective tissue and their branches become so dense that when cut across they appear macroscopically as nodules. In many of the lobules, blood vessels, bronchi and alveoli have become obliterated and in the fourth stage nothing remains of the original lung tissue. Large blood vessels and bronchi are surrounded by dense scar tissue presenting lacunae and clefts where alveoli once were. These masses of scar tissue are poorly nourished and often undergo degeneration and liquefaction in their center. In nearly all of the cases that go on to cavity formation, tubercle bacilli are found in the scar tissue. However, there are often none of the histological features of tuberculous tissue, and this has led some observers to regard them as saprophytic invaders which have had no hand in the development of the pathological picture. In the early and middle stages of the disease it is common to find the characteristic changes of both silicosis and tuberculosis side by side.

In pneumonoconiosis the bronchial lymph glands always show marked changes. In the early stages they are deeply pigmented and later they become enlarged and fibrotic. In late stages they may soften and sometimes they rupture into contiguous structures.

Symptoms

Pneumonoconiosis gives symptoms only (1) when the consequent fibrosis is advanced or (2) when there is an associated infection. The inhalation of dust of any kind causes irritative symptoms in the upper respiratory tract. There is coryza, sneezing and cough. Workers in a dusty atmosphere lose these symptoms quickly and then experience nothing unusual until advanced fibrosis has developed. Even when there is extensive dust deposit and well marked general diffuse fibrosis the lung function may be normal and the patient unaware of any disorder. The condition could not be diagnosed except by X-ray examination or at autopsy. Changes in the lungs seldom proceed beyond this point except following exposure to silica, and damage to the lungs is nearly always proportionate to the amount of silica in the inhaled dust. Anthracosis never causes pulmonary symptoms unless the coal dust is mixed with silica. The most extensive pulmonary changes are found among the gold miners in the Transvaal and the zinc miners in southwestern Missouri. Where workmen are constantly exposed to large quantities of silica, symptoms of fibrosis may come on after a few years; under all other circumstances they come on extremely slowly and insidiously.

Cough is the earliest and most constant symptom. At first it is a dry, hacking cough, often occurring only in the morning. Later sputum develops, at first tenacious, glairy, grayish in color from the contained dust. In coal miners the sputum is often black. If the dust contains colored particles the sputum is often distinctively colored, red if the dust contains oxide of iron, blue if it contains ultramarine blue, etc. A characteristic slaty blue color is often diagnostic in zinc miners. These patients are susceptible to bronchitis, and during attacks the sputum may be mucopurulent and abundant. Hemoptysis is common in silicosis, especially when there is an associated tuberculosis. When cavities occur the sputum is abundant, mucopurulent and often fetid. In later stages shortness of breath gradually develops. Sometimes, especially in silicosis, it is the earliest symptom and precedes cough. At first there is a little dyspnea on exertion which gradually increases and may finally terminate in extreme dyspnea even when the patient is at rest. The dyspnea is often associated with bronchitic wheezing and may be paroxysmal resembling asthma. Pleuritic pains are common. In late stages the symptoms of myocardial insufficiency may supervene for the same reasons as in emphysema.

The examination of the patient in the early stages gives no abnormal signs to attract attention to the condition. In later stages the chest may be full and emphysematous in type, but usually there is retraction which may be more marked on one side. Expansion is limited and the chest may be more or less fixed. The percussion note shows no characteristic change, it may be hyperresonant in some places, dull in others. Over cavities, when these are present and located near the surface, the note is tympanitic. The breath sounds are diminished in intensity in some places, in others rather smooth and blowing as in emphysema. When cavities are present they show the usual changes on auscultation. All manner of râles are present in the late stages.

The X-ray examination, although not distinctive, gives the most valuable aid to diagnosis. It often indicates the presence of advanced pneumonoconiosis when it could be detected by no other means. In the first stages the hilus shadows are broad and deep, and the bronchial tree shadows are thickened and intensified. The linear markings are prominent. The excursion of the ribs and diaphragm may be restricted. In a later stage the lung fields appear densely mottled. This mottling appears earlier, as a rule, on the right than on the left side, and usually first at the level of the hilus. Later it becomes equally distributed on the two sides, and usually more marked in the middle zone than at the apex or base. As the condition progresses, the mottling is replaced by the dense shadows of fibrous bands that form through the lung, and the lungs may appear uniformly hazy from pleural thickening. The diaphragm is usually deformed.

The fibrosis of pneumonoconiosis cannot be definitely distinguished from tuberculous fibrosis. Only the history and the negative sputum may separate the two. Bizarre symptoms may be caused by the enlarged, indurated bronchial glands, especially when they soften and discharge into surrounding organs. Compression of the esophagus, diverticulum of the esophagus, bronchopneumonia and gangrene following rupture into a bronchus, pericarditis, compression of the trachea or bronchi, narrowing or obliteration of the vena cava, of the azygos veins, and of the pulmonary artery, and recurrent laryngeal paralysis have been described.

The Relation of Pneumonoconiosis to Pulmonary Infections, Especially to Tuberculosis

There is wide difference of opinion concerning the role that pneumonoconiosis plays in predisposing the lungs to infection. Dusty atmospheres contain usually many bacteria, and it seems reasonable to suppose that bacteria are carried into the lungs with the dust and that the changes caused by the dust might facilitate the implantation of the bacteria. If for the moment we leave tuberculous infection out of consideration, actual experience does not lend strong support to this view, although the evidence is differently interpreted. For instance, pneumonia is especially prevalent among the Transvaal gold miners, who suffer also extensively from silicosis. However, it is the new comers to the mines who most often develop pneumonia, and the incidence of the disease bears no relation to the degree of silicosis. Secondary infections are common in pneumonoconiosis as they are in all chronic respiratory diseases, but hardly more common than in other forms of fibrosis. Bronchitis is always present when the condition is at all advanced, and bronchial infection no doubt plays an important part in the development of bronchiectasis.

It has always been noted that pulmonary tuberculosis is prevalent among the workmen in dusty trades. The conditions that enter into an analysis of the situation are very complex. Hoffman has gone into the matter in great detail. That dust itself is not the only important factor to be considered is shown by the prevalence of tuberculosis in trades where dust causes no, or only slight, pulmonary changes, as in tobacco workers, and by the very low mortality rate for tuberculosis among coal miners. On the other hand, the excessive incidence of tuberculosis among masons, stone-cutters, gold miners and others exposed to siliceous dust, points clearly to some relation between the pulmonary damage and the tuberculous infection. A few of the important elements entering into the discussion of the question are the following:

1. It is important to distinguish between tuberculous infection of the lung in the sense of a localized focus of tuberculosis, which is incidental to some other pulmonary disease, and pulmonary tuberculosis in the sense of an advancing disease of the lungs responsible for the symptoms. In certain

types of pneumonoconiosis, especially in silicosis, tubercle bacilli are often found in the fibrous areas without associated tuberculous tissue. Therefore, although tubercle bacilli are present, they may add little of importance to the existing fibrosis or to the clinical symptoms. If tuberculous lesions develop, as they frequently do, in late stages of silicosis, they add to the symptoms by expediting liquefaction and cavitation. All observers comment upon the fact that persons with silicotic lungs develop tuberculosis at an unusually late period of life, and that the disease, when it develops, is characterized by the absence of the usual constitutional symptom of tuberculosis and shows no tendency to spread rapidly. These facts, it seems to me, may be satisfactorily explained by the local conditions in the lung without discussing whether pneumonoconiosis raises or lowers resistance to tuberculous infection. In the sense that implantation of the tubercle bacillus is facilitated, resistance is lowered, in the sense that when the tubercle bacillus enters the tissue, its effects are restricted and hemmed in, resistance is raised. No doubt the condition of the lymph channels and circulation plays an important part in these relations. Under healthy conditions, when a few tubercle bacilli enter the lung, they are quickly transported through the lymph channels to the bronchial glands. When the lymph channels are occluded the tubercle bacilli remain where they fall and have a better opportunity to gain a foothold. However, even though they survive, the circulatory conditions in the tissue may prevent a satisfactory growth. In this manner, one may explain the frequent association of pulmonary tuberculosis and pneumonoconiosis, the absence of extensive tuberculous disease and the fact that tuberculosis nearly always affects the fibrotic portions of the lungs and only seldom the portions with patent alveoli.

2. Undoubtedly exposure to tuberculous infection is an important factor in determining the incidence of tuberculosis in a trade. Of course tuberculous infection cannot arise without exposure to tubercle bacilli, so that every person who contracts the disease must have been exposed. But the frequency and the intensity of exposure must play an important part in determining the development of tuberculous disease. In some trades that are not very dusty and in which the dust does not provoke a marked reaction in the lungs, the high incidence of tuberculosis must depend upon either massive infection or lowered bodily resistance. In determining these two factors a detailed investigation must be made into the working conditions in the shops, the degree of exposure in the home, the character of the dwelling and the food, indeed into every factor of the worker's life in and out of the shop. To these factors some would ascribe all of the blame for the high morbidity from tuberculosis, even in trades causing pneumonoconiosis. Thus Lord suggests that the high incidence of pulmonary disease

among marble and stone-cutters may be due to the unsanitary conditions of their work rather than to the direct effect of dust on the lungs, and Beattie believes that the prevalence of tuberculosis among grinders is due to the habit of spitting on the wheels and hands, thus contaminating the water used by all. It cannot be questioned that appropriate hygienic regulation of the work and the living conditions of workmen will greatly reduce the incidence of tuberculosis, but exposure being granted, it is possible that the changes caused in the lungs by certain dusts may definitely predispose to tuberculosis. That this is really the case seems to me to be established by the relative incidence of tuberculosis in different dusty trades.

3. No statistical evidence could be more impressive than the disproportion between the incidence of tuberculosis among miners exposed to siliceous dust and miners exposed to coal dust. In silicosis the incidence of tuberculosis increases also very strikingly with the stage of the disease. Coal miners and workers in lime and cement display such a low tuberculosis morbidity that the inhalation of coal and lime dust has been seriously proposed as a treatment for tuberculosis. I do not wish to imply that anthracosis and calicosis really enhance resistance to tuberculosis, but surely the inhalation of coal or lime does not increase the danger of developing the disease. In this respect dusts seem to vary in proportion to their power of inciting fibrosis, and a mechanism by which to explain satisfactorily this difference has been proposed.

4. Finally there are certainly difficulties in the way of estimating the accuracy of statistics bearing upon the incidence of tuberculosis in dusty trades. In the first place there is a confusion in terms. Pneumonoconiosis is frequently termed phthisis even when tuberculous infection is absent. Miners' phthisis is a frequently used term even in the absence of tuberculosis. Finally, the distinction between the two conditions is often difficult, and the diagnosis bronchitis, asthma or bronchopneumonia masks many deaths from tuberculosis, while tuberculosis is often assumed to be present from the symptoms when the tubercle bacillus is really absent.

Treatment

There is no specific treatment for pneumonoconiosis. The dust accumulated in the lungs cannot be removed. All of the emphasis must be put upon prevention, the prevention of dust inhalation and a proper regulation of the working conditions and living conditions of the workmen. Persons with a tendency to respiratory infections should not be permitted to work in dusty trades. The first onset of pulmonary symptoms in those engaged in dusty occupations should be the signal to abandon the work. Although the damage done cannot be remedied it may be held in check by avoiding further exposure to dust, and thus the late manifestations of extensive fibrosis may be prevented. Complications, namely bronchitis, bronchiectasis, myocardial insufficiency must receive appropriate attention.

Animal Parasites*

Echinococcus Disease of the Lungs

Echinococcus disease of the lungs is a rare malady in this country and is encountered almost exclusively in foreigners. It occurs frequently in Australia and in Sweden. The intestinal parasite, tenia echinococcus, occurs in dogs and in many wild animals. Sheep, cattle and swine are the usual intermediate hosts. The infection in man is always contracted from dogs, and dogs herding sheep are most frequently infected. The tenia echinococcus is a small parasite measuring from 4 to 5 mm. in length. It consists of three segments, the terminal, ripe segment containing several hundred eggs. When these eggs enter the intestinal canal the embryo is set free and with the aid of its six hooks bores a way through the intestinal wall. In most instances it enters the portal circulation and lodges finally in the liver. Occasionally it is carried directly to the lung, but by exactly what channel is unknown. It has been suggested that it may first reach the liver and then the lung by piercing the diaphragm, that it may pass through the esophagus and into a branch of the vena cava and thus through the right heart to the lung, or that it may pass through the rectum and enter a branch of the inferior hemorrhoidal vein. In secondary echinococcus of the lung, invasion may occur by extension from a contiguous cyst or by metastasis. Most hydatids of the lung are primary, and usually when the lungs are infected cysts are not found in other organs.

Pathological Anatomy

Echinococcus cysts may be found anywhere in the lung, but most commonly are situated in the right lower lobe. They may occur at any age, but most often between twenty and forty years. They vary in size from that of a pea to a child's head. Not infrequently the cysts are multiple.

The usual type is the unilocular cyst. It may be sterile (acephalocyst) or contain numerous daughter cysts which may develop within the mother cyst (echinococcus hydatidosis endogenus), or between the cyst and the fibrous capsule that walls it off from the lung parenchyma (echinococcus hydatidosis exogenus). The capsule is usually very thin, but in long standing cases and especially about cysts that have ruptured it may be thick and leathery. In the neighborhood of the cyst the lung tissue may be normal, but induration often occurs and sometimes abscess and gangrene.

When the cyst grows to a large size it usually ruptures, emptying its contents into a bronchus, the pleural cavity or into the lung. Occasionally it ruptures into the pericardium, the spinal canal or through the diaphragm. Following rupture the cyst may shrivel up, leaving a pasty mass containing lime and cholesterin, which is finally replaced by scar tissue. More often the cyst becomes infected and a chronic abscess is formed. Rupture into the pleura is usually followed by empyema. A pyopneumothorax may develop.

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* For descriptions of animal parasites, see Vol. V.

The contents of the cyst consist of a clear, opalescent fluid rich in sodium chloride, of a low specific gravity and containing very little albumin. Microscopically the characteristic hooklets are seen. Multilocular echinococcus cysts seldom occur in the lung.

Symptoms and Signs

During the early period while the cyst is still small no symptoms are present. Later the patients have cough, hemoptysis, dyspnea, pleurisy and thoracic pain or oppression. Sputum is absent or slight unless there is an associated bronchitis. The symptoms strongly suggest pulmonary tuberculosis, but the patients are usually in good physical condition, and there is little or no fever. Special emphasis should be put upon hemoptysis, which is a constant symptom. It is usually small in amount and frequently repeated, but occasionally the bleeding is large and a brisk hemorrhage may be the first symptom of pulmonary disease. After such a hemorrhage there may be a period of many months or even years before further symptoms appear. In the one definite case I have seen, a young man in good health had a large hemorrhage. After recovery he was well for nearly a year, when he entered the hospital again with profuse hemoptysis. On this occasion masses of the cyst membrane were expectorated. In the early stage the physical examination may reveal only slightly abnormal signs. The side affected may be enlarged and the respiratory movements restricted. The percussion note may be resonant, dull or flat, depending upon the location of the cyst. The breath sounds and voice sounds are diminished in intensity. In uncomplicated cases there are no râles.

As the cyst enlarges, all of the symptoms, especially pain or thoracic oppression, become more prominent. If the cyst remains intact and does not become infected, the symptoms of a large thoracic tumor develop, namely, bulging of the chest wall, dyspnea, and displacement of the mediastinal organs. However, before the cyst reaches such a large size it usually becomes infected or ruptures. If the cyst becomes infected the patient develops fever and the usual symptoms of abscess. When rupture occurs in the pleural cavity an empyema forms which may heal completely by drainage or remain open for an indefinite period. Not infrequently pneumothorax occurs, which may be accompanied by stormy symptoms and be quickly followed by death. If the cyst perforates into a bronchus it usually provokes intense coughing and symptoms of suffocation. The characteristic cyst contents are expectorated and there is often at the same time profuse hemoptysis. After rupture the cyst may collapse and the lesion heal, but usually suppuration occurs and a chronic lung abscess results.

With the rupture of the cyst very interesting symptoms of intoxication occur similar to the symptoms of protein hypersensitiveness. Usually a widespread and intense urticaria is the only hypersensitive symptom, but there may be cyanosis, dyspnea, chills, collapse, vomiting and convulsions. In some instances death has quickly followed the onset of these symptoms.

The X-ray picture of echinococcus cyst is very characteristic and is the most important aid to diagnosis. A similar picture occurs only in dermoid cysts. The shadow is very deep, round, and absolutely clear cut. It looks as though a cannon ball had been placed in the chest. This characteristic picture is not always present. The borders may be more indefinite when infection has occured and there are changes in the surrounding lung tissue.

The blood shows usually a moderate leucocytosis and a decided eosinophilia, sometimes as high as fifty per cent. However, in a certain number of the cases, eosinophilia is absent. The blood serum occasionally gives a precipitin reaction with the fluid from a hydatid cyst. Of more practical importance is the complement-fixation test, using cyst fluid as antigen. It is said to be positive in a large proportion of the cases.

The diagnosis of echinococcus cyst is difficult because instances are so rarely encountered. If the condition is thought of, the history, the physical signs, the characteristic X-ray picture, the eosinophilia and the complement-fixation test make a satisfactory diagnostic picture. In the early stages it is usually confounded with tuberculosis. The absence of constitutional symptoms and of the usual physical signs of tuberculosis, together with the X-ray plate and the blood examination, should clearly separate the two. A large echinococcus cyst in the lower lobe may simulate a pleural effusion. A careful physical examination should distinguish between the two. If it does not the X-ray picture usually will. The blood may be a further distinguishing feature. The distinction between echinococcus cyst and tumor may be difficult. The presence of eosinophilia and a positive complement-fixation test would decide for echinococcus. The same factors and the X-ray would help to distinguish an infected cyst from an abscess. A hydatid cyst of the liver rupturing into the lung may go unrecognized until discovered at operation. A correct diagnosis has often been made by examination of the fluid obtained by thoracentesis. A clear watery fluid, of a low specific gravity, containing much salt and only a little albumin is characteristic.

Hooklets are also frequently found. However, thoracentesis should never be done for diagnostic purposes. Rupture of the sac nearly always ensues and death frequently follows.

Treatment

There is no medical treatment for echinococcus disease aside from general supporting measures and the use of symptomatic remedies. Some cases heal spontaneously after rupture of the sac, but the result is always doubtful and the larger proportion of the cases die. When an unruptured cyst is favorably located operation offers an excellent chance of recovery. Even after the cyst has become infected or has ruptured, operation offers a much better chance of recovery than expectant treatment. Some patients have been cured by simple puncture, but the practice is very dangerous and should not be used.

Pulmonary Distomatosis (Lung fluke disease)

The disease is common in China, Formosa and Japan. It exists less frequently in Korea and the Philippine Islands. Several cases have been described in the United States, occurring in foreigners. The disease affects many animals, dogs, cats, swine and cattle. The organism was first observed in the lungs of a tiger.

The worm is a brownish red, oval fluke with rounded ends, measuring from 8 to 16 mm. long and 4 to 8 mm. wide. The eggs are oval, of a brownish color, larger than the eggs of most other parasites, measuring from 0.08 to 0.1 mm. in length and from 0.05 to 0.1 mm. in width. They may be seen with the unaided eye as minute brown specks. The membrane is very thin and there is an operculum at one end. The life history of the worm is not fully known. It is thought that the parasite uses fish and snails as intermediate host, and that animals and man are infected from these.

Pathology

The parasite and the eggs may lie free in the smaller bronchi, but are usually encased in a firm, fibrous tissue capsule. The cysts thus formed contain a brownish caseous mass consisting of numerous eggs, mucus, blood, leukocytes, disintegrated cells and Charcot-Leyden crystals. These cysts rupture into bronchi and frequently communicate with one another. They may be scattered widely through the lungs and form hard, dense nodules which project above the surface when they are situated beneath the pleura. The distoma or its eggs have been found also in the brain, the diaphragm, the mesentery, the liver, the orbital cavity, the eye lid, the cervical glands, etc.

Symptoms

The only characteristic symptom is the occurrence of the eggs and occasionally of the fluke in the sputum. The patients have cough and expectorate a yellowish or brownish sputum having the character of the cyst contents. Hemoptysis is common. It is usually small in amount and frequently repeated, but copious hemorrhage sometimes occurs. Patients who bleed freely develop a serious anemia of which they may die. The general health is little affected unless there be anemia. The patients as a rule have no fever. The physical signs are not distinctive, usually they are simply the signs of bronchitis. Retraction of the affected side may occur when there is pleurisy. There may be patches of impaired resonance, harsh or impure breath sounds and moist râles. It is said that if patients remove from an infected area they usually recover. The disease may be present for twenty years and longer. In such instances reinfection probably occurs. Death is generally due to anemia or to brain metastasis.

Treatment

There is no special treatment for the condition except removal from the infected area. Efficient prophylaxis cannot be practised until the life history of the parasite is fully known.

Tumors of the Lung

Carcinoma is the commonest tumor of the lung. Secondary growths are observed more frequently than primary. These secondary growths may occur by direct extension from contiguous carcinomata or as metastases from distant tumors. Carcinoma of the breast frequently invades the pleura directly, less commonly through metastasis to the mediastinal, bronchial, subclavian and supraclavicular lymph nodes. Pleural effusion is usually the first evidence of this invasion. Sometimes the growth extends directly to the lung, causing little pleural change. Carcinoma of the stomach may extend through the diaphragm and invade the lung in a similar way. Under these circumstances pleural involvement is far more common than pulmonary. The pleural or pulmonary symptoms may dominate the clinical picture and the stomach growth be unsuspected.

Of carcinomata that metastasize to the lung, breast and kidney tumors are clinically the most important, although carcinoma in any organ may give lung metastases. These metastases are frequently small and even though they may be numerous they are usually overlooked clinically. Occasionally, miliary carcinomatosis of the lungs occurs. A lung growth may be the first evidence of recurrence of breast cancer removed apparently successfully years before. The association of obscure or unusual pulmonary symptoms and signs with one or more nodules in the bones is peculiarly characteristic of hypernephroma. The presence of this tumor is sometimes predicted from these remote manifestations before there is any local evidence of a renal growth. Primary carcinoma of the lung is an uncommon disease. Among 16,578 cancer autopsies, 168 lung cancers were recorded (Ewing). Among 46,169 autopsies, primary cancer of the lung was found in 105 (Lord). From the histogenetic standpoint, three types of pulmonary carcinoma are recognized, arising respectively from the bronchial epithelium, the bronchial mucous glands and the alveolar epithelium.

Carcinomata arising from the bronchial epithelium often cause bronchial obstruction and bronchiectatic cavities; they seldom cause a diffuse tumor of the lung. When the growth has reached large size it often forms a mass at the hilus of the lung, surrounding the large bronchi, with projections along dilated bronchi, which form large bronchiectatic cavities in the mass of cancer tissue. Histologically the tumors consist of squamous or cylindrical cells in alveolar arrangement. In advanced stages, both the character of the cells and their arrangement vary, especially in the cylindrical cell type.

Carcinoma arising from the mucous glands begins in the large bronchi. A number of small growths have been described of glandular structure with mucoid secretion, beginning in the walls of the bronchi and covered by intact bronchial epithelium. These typical mucous gland tumors infiltrate the bronchial wall, often causing bronchial obstruction. As the tumor spreads by direct growth and by metastasis the characteristic gross and histological picture may become obscured. The secretion of abundant mucus is a very characteristic feature of mucous gland growths, although it is not restricted to them.

Carcinoma arising from the alveolar epithelium produces infiltrating masses which often spread rapidly, involving a lobe or larger areas, and somewhat resemble organizing pneumonic consolidation. The air cells are filled with epithelial cells, cuboidal, cylindrical or squamous in type. Occasionally the tumors have a papillary structure. At times instead of a diffuse growth multiple nodular tumors are formed.

All lung cancers produce marked and often early pleural involvement. In late stages numerous metastases occur. Occasionally a small lung tumor that gives no local symptoms may cause widespread metastases. Any organ or tissue may harbor metastases, but the lymph glands, liver, bones and kidneys are most often invaded. In the lungs tumor growth may cause cavities, bronchiectasis, erosion of blood vessels, sometimes with fatal hemorrhage, and it may be accompanied by bronchopneumonia, empyema, or gangrene.

Secondary sarcoma of the lung is less common than carcinoma, but the proportion of sarcomata metastasizing to the lung is greater. As in carcinoma multiple tumors may occur that give no symptoms. At other times, large infiltrating masses are produced. Sarcoma of bone and melanotic sarcoma almost regularly metastasize to the lungs. The secondary tumors do not always faithfully reproduce the structure of the primary growth.

Primary sarcoma of the lung is rare, probably even rarer than reports lead one to believe, because many tumors reported as sarcoma have been insufficiently studied. Certain inflammatory changes in the lungs may simulate sarcoma in structure, and certain areas of carcinomata are indistinguishable from sarcoma. Pulmonary lymphosarcomata must always be secondary to tumors arising in lymph glands or in the thymus. The diffuse spindle-celled tumor is the most characteristic and the most common of lung sarcomata. It usually causes a large infiltrating mass, but there may be smaller, multiple tumors. Peribronchial sarcomata are described which presumably arise from the bronchial walls. They are made up of small round cells and resemble lymphosarcomata, and since the bronchial glands are always involved they may be extensions of gland tumors. It is difficult to distinguish these growths from a certain type of carcinoma. Large round cell tumors similar to the spindle-cell growths are described.

Symptoms

The symptoms of carcinoma and of sarcoma of the lung are so much alike that the two conditions can never be surely differentiated clinically. Nor can the various types of carcinoma be separated. Their symptomatology is so similar that all varieties of malignant growth may conveniently be grouped together. In late stages of the disease the correct diagnosis can often be made with reasonable certainty, but in early stages the true nature of the process almost uniformly escapes detection. The symptoms may appear under a variety of aspects, chiefly (1) as a chronic pulmonary inflammatory disease; (2) as a chronic pleurisy with effusion; (3) as a localized tumor.

The commonest group of symptoms produced by growths resemble those of a chronic pulmonary inflammatory disease, and the usual diagnosis is pulmonary tuberculosis, chronic pneumonia, unresolved pneumonia, chronic non-tuberculous pulmonary disease, etc. It cannot be too much emphasized that tumors of the lung are nearly always accompanied by fever. It is the presence of fever more than of any other symptom that usually misleads the physician. Sometimes the fever is slight, sometimes periodic, more commonly high and continuous. Fever, cough, sputum and the signs of pulmonary infiltration nearly always lead the physician to assume that the symptoms are due to inflammatory infiltration. Since cancer not infrequently develops in a tuberculous lung, the presence of tubercle bacilli in the sputum is no sure protection against this error. The additional symptoms that should strongly suggest growth even though fever be present, are pain, unusually marked, and rapid loss of weight and strength, dyspnea and peculiarities in the physical signs.

The next most common group of symptoms produced by growth are those of a chronic pleurisy with effusion. The sympt ms usually come on insidiously with pain in the side and dyspnea, the effusion being discovered on physical examination. The rapid reaccumulation of fluid after frequent aspiration, especially if the fluid becomes progressively more and more bloody, is very characteristic of tumor. However, tuberculous pleurisy may behave in the same way, and I have seen a pleural effusion due to pleural growth disappear after one or two aspirations. There is no way to distinguish primary pleural growths from pleural growths secondary to lung tumors.

The symptoms of localized tumors are the least common manifestations of a lung growth. These symptoms are usually mediastinal and are as often due to enlarged metastatic mediastinal glands as to the primary lung tumor. Cases are described in which bronchial stenosis is a prominent symptom. Behier's sign, which consists of a curious broken, whistling sound heard in the interscapular area on inspiration, is said to be peculiar to the condition. Although I have sought for this sign, I have never discovered it. Paralysis of the recurring laryngeal nerve, stridor and rarely a tracheal tug may also be found. Therefore the cardinal symptoms of pulmonary growths are (1) pain, (2) dyspnea, (3) cough, (4) sputum, (5) fever, (6) pleural effusion.

Pain is by no means a constant symptom, but when present is an important aid to diagnosis. Pain is usually most severe when the pleura is involved. It is peculiarly persisting and does not stop with the occurrence of effusion, nor after the length of time when in tuberculous pleurisy pain usually disappears. The occurrence of severe, continuous pain in the absence of pleurisy is very characteristic of a growth. Constant boring pain with indefinite or unusual pulmonary symptoms should at once awaken the suspicion of a growth. At times pain is the most distressing symptom of which the patient complains; at other times, pain is entirely absent.

Dyspnea is a common symptom. It may be the prominent symptom when there is a large pleural effusion. Sometimes it is caused by pressure upon a main bronchus or the trachea, either by the primary tumor or by enlarged mediastinal or bronchial glands. However, it must be remarked that there may be complete occlusion of a main bronchus without dyspnea. In late stages when the lung is extensively involved dyspnea is nearly always marked.

There is nothing peculiar about the cough of lung growth. It may be dry and unproductive as it often is in pleural growth, or when there is pressure upon the trachea. It is seldom absent for any length of time, and may be harrassing before definite pulmonary signs are discovered.

Sputum may be absent for some time after pain, dyspnea and cough have appeared. In later stages of the disease it is usually abundant. There is nothing absolutely characteristic about the sputum of tumor. Sometimes it is the mucopurulent material commonly found in various pulmonary inflammations. The only peculiarity frequently associated with growth is the presence of blood. This is usually dark in color and intimately mixed with the mucopurulent material. Sometimes the sputum has a color and consistency that has been likened to currant jelly. The comparison is appropriate and this character of sputum is seldom found in other conditions. While bloody sputum is in no way characteristic of lung tumors, the persistence of bloody sputum for a long time, for weeks and months, is almost peculiar to it. Frank hemoptysis is quite rare.

Not infrequently large masses of tumor tissue are expectorated. The sputa should always be carefully searched for particles of tissue, for these, when fixed and sectioned, will often settle a doubtful diagnosis. Even when no particles are visible to the naked eye nests of tumor cells may be found under the microscope. Lenhartz has emphasized the diagnostic importance of large strongly refractile spherical bodies filled with fat globules. These presumably represent degenerated tumor cells. Lenhartz thought they occurred only in malignant disease, but they have been found also in other conditions.

As I have previously noted, fever is commonly present in malignant disease of the lungs. Sometimes it is only slight, not exceeding 100° F. in the evening; at other times it is irregular and continuous, going to from 102° to 104°F. each day for weeks and months; at still other times fever comes in recurring attacks. Physicians seem always to point to fever as a symptom excluding growth. In my experience it is the exception to find it entirely absent.

The pleura is so commonly involved in tumor of the lung that pleural effusion is one of the chief symptoms of the condition. Occasionally pneumothorax occurs and may even be the first important symptom. Aspiration may yield important evidence. The hard resistant sensation often experienced on introducing the needle and piercing the pleura should suggest growth, although tuberculosis of the pleura may cause the same sensation. Often when fluid is anticipated on account of the flatness and absent breath sounds none is obtained. Small particles of tissue may remain in the lumen of the needle and microscopical examination of these may reveal tumor cells. If fluid be obtained it is frequently bloody. Careful examination of the sediment may reveal tumor cells. Pick recommends thorough centrifugalization of the fluid, fixating of the sediment in formalin and alcohol and imbedding in paraffin.

Physical Signs

The physical signs of tumor of the lung depend upon the size and location of the tumor. If the pleura is markedly involved and there is pleural effusion, the signs of the pulmonary growth may be obscured. If the tumor is located within the lung, there may be no unusual physical signs, or at most a little dullness and diminished intensity of the breath sounds. If the tumor is situated near the hilus of the lung or if there is extensive metastasis in the mediastinal glands the signs and symptoms may be those of a mediastinal tumor. The growths that give the most characteristic signs are those that reach the periphery of the lung without causing pleural effusion. The excursion of the affected side is markedly restricted and often out of proportion to the apparent area of lung involvement. The percussion note is very dull and the dullness is often well localized. These signs situated in unusual positions are strongly suggestive of tumor. For instance a circumscribed area of dullness below a clavicle and near the sternum with a resonant note above the clavicle and no dullness over the upper lobe behind is very characteristic of tumor. A localized area of dullness or flatness below the angle of the scapula with a resonant area at the base is likewise characteristic. Over these areas of dullness the breath sounds may be intensely tubular in quality, although more commonly they are absent or greatly diminished. Fremitus is usually absent or but faintly appreciable. Râles are usually absent and are seldom abundant. Therefore an area of marked circumscribed dullness in an unusual position with absent fremitus, breath sounds and râles is strong evidence in favor of a growth.

While the X-ray lends valuable aid to the diagnosis of lung tumor, its value in primary tumors is not nearly so great as one would anticipate. Secondary growths are usually portrayed as multiple, sharply outlined shadows that have a characteristic appearance. Their presence can often be diagnosed from the roentgenogram when symptoms and physical signs are absent. Pleural effusion, of course, obscures the affected side by a dense shadow which makes it impossible to discern the condition of the lung beneath. When the tumor is intrapulmonary the shadows are by no means characteristic and are often misleading. Even when a diagnosis of lung tumor may be made from the other clinical evidence, the roentgenologist will often report pulmonary tuberculosis, unresolved pneumonia, localized pleural effusion or non-tuberculous infiltration. I have seen three instances of such disagreement in all of which the subsequent course proved the clinical impression to be correct. In a number of other instances in which the symptoms of a beginning tumor were misinterpreted, the X-ray lent full approval to the misinterpretation. I cite these experiences not to belittle the value of X-ray in the diagnosis of lung growths, but to warn physicians against too implicit a reliance upon the X-ray definitely to verify or disprove the presence of a tumor.

The course of primary malignant disease of the lung is variable. The duration of life after symptoms appear is usually from six months to two years. If the tumor compresses the trachea, dyspnea and stridor may be followed by suffocation. Fatal hemoptysis may occur but is very uncommon. Loss of weight and strength is usually marked and cachexia nearly always striking. Complications play an important part in coloring the clinical picture. The pleura is commonly involved and if effusion occurs it is usually peculiarly persisting. Not infrequently the pleural effusion is infected and an empyema develops which may obscure the evidence of a primary lung growth. The carcinomatous mass may become gangrenous, which is always a rapidly fatal complication. Areas of bronchopneumonia commonly surround the growth and complicate the symptoms with the symptoms of an inflammatory reaction. Bronchitis and emphysema may obscure the evidence of tumor. Dyspnea, cough, bloody sputum, fever and rapidly developing cachexia is the commonest group of symptoms.

Treatment

There is at present no satisfactory treatment for malignant disease of the lung. Our only reasonable hope is that with the rapid development of lung surgery diagnosis will improve apace. Early cases may then be successfully operated upon. Diagnosis is at present so difficult that even advanced cases are usually overlooked.

Benign tumors of the lungs, excepting dermoid cysts, have little clinical interest. They seldom give symptoms and are discovered accidentally upon X-ray examination or at autopsy. Fibromata, lipomata and osteomata occur.

Dermoid Cysts of the Lung

Dermoid cysts rarely occur in the lung; usually they begin in the upper anterior mediastinum and involve the lung by compression or by rupturing into it. They vary in size from tumors as big as a walnut, discovered accidentally at autopsy, to masses as large as a child's head, containing as much as three liters of fluid. The walls are usually thin but densely adherent. The cysts almost regularly contain hair, and in the walls, bone, cartilage, teeth, glands and other structures are commonly found. In about half of the cases the cyst ruptures into a bronchus. Less commonly it ruptures into the pleural cavity, the pericardial cavity, the lung, the aorta, the vena cava and externally through the skin.

The *symptoms* are extremely varied. They usually begin after puberty, in over fifty per cent. of the cases the first symptoms appear between the twentieth and thirtieth years. Sometimes the mediastinal mass is discovered before symptoms occur; at other times when the first symptoms are associated with rupture of the cyst, grave manifestations may suddenly appear. The chief symptoms that occur are dyspnea, pain, pleural effusion, cough and sputum. Recurring hemoptysis is common. When the cyst ruptures into a bronchus, sputum is usually abundant. In from one-quarter to one-third of the cases hair is found at some time in the sputum. Horny epithelial cells, fat droplets and cholesterin crystals may be found in the sputum and give the clue to the correct diagnosis. After symptoms appear the disease usually progresses rapidly and death occurs in from four to five years. Sometimes death occurs very quickly after the symptoms of rupture appear; at other times symptoms last for many years, in one instance for forty-four years.

The *physical signs* are those usually associated with mediastinal tumor. When the cyst is very large and particularly when it is situated in the posterior mediastinum, it may simulate a pleural effusion. After rupture has occured the signs may be very confusing and lead to great difficulty in diagnosis.

Dermoid cysts may be distinguished from malignant disease by the age incidence, the longer duration of symptoms and the absence of cachexia. Pressure symptoms are less common with dermoid cysts than with malignant growth or aneurysm. It is often difficult to distinguish it from pleurisy with effusion, encapsulated empyema and abscess.

The only treatment is surgical. Many cases have been operated upon with benefit. The usual procedure is to incise and drain the cyst. The whole tumor was successfully removed in one instance.

INFLAMMATORY DISEASES OF THE LUNGS*

BRONCHOPNEUMONIA

The terms bronchopneumonia, lobular pneumonia, catarrhal pneumonia, which are used synonymously, are employed to distinguish certain types of pulmonary inflammation from a nearly related form of pulmonary inflammation, designated lobar or croupous pneumonia. There are excellent reasons for wishing to make this distinction both from an anatomical and a clinical standpoint, but the terms proposed do not embrace these reasons. Catarrhal pneumonia is an obsolete term, fortunately but little used; it refers to the association of areas of consolidation with bronchial catarrh. Lobular pneumonia is a purely anatomical concept, indicating an important, but not the most important, nor yet a constant, distinguishing feature.

* Lobar pneumonia is discussed in Vol. V, Chapter IX.

Bronchopneumonia emphasizes the important role of bronchial inflammation and the spread of the infection from the bronchi to the surrounding alveoli. All of these terms are unsatisfactory because bronchopneumonia is not always secondary to bronchitis or bronchial catarrh, it is not always lobular in arrangement, and the really important reason for distinguishing lobar and bronchopneumonia is not even suggested. The really important reason is the difference in the clinical course of the two diseases. Lobar pneumonia is essentially a primary disease, bronchopneumonia is essentially a secondary disease; lobar pneumonia has a characteristic clinical course, bronchopneumonia has a protean clinical course; lobar pneumonia has a uniform pathological picture, bronchopneumonia has a varied pathological picture; lobar pneumonia is due to a definite and constant bacterium, bronchopneumonia is due to many different organisms. In a word, lobar pneumonia has as its distinguishing mark the characters of a specific infectious disease, bronchopneumonia lacks these characters entirely. Unfortunately many exceptions occur to these generally valid statements. Certain cases of primary bronchopneumonia resemble clinically the classical picture of lobar pneumonia, and certain instances of lobar pneumonia are indistinguishable clinically from bronchopneumonia. While most cases of lobar pneumonia are due to the pneumococcus, other organisms may cause lobar consolidation; the specific bacterium of lobar pneumonia is as well the most frequently found organism in secondary bronchopneumonia. There is therefore no satisfactory basis upon which to classify pneumonias. Whether one choose a clinical, an anatomical or a bacteriological basis, one will invariably consider under each heading conditions which for some other reasons should be considered under the other heading. In the face of this unsatisfactory state of affairs the division of the pneumonias into lobar and bronchopneumonia serves as well as any other division that could be proposed, provided we use the terms to designate clinical as well as anatomical distinctions. I wish only to emphasize that while we clinically hold to the concept of lobar pneumonia as a specific infectious disease, circumstances compel us to consider also under this caption forms of lobar consolidation that do not properly belong there, while we group under bronchopneumonia a heterogeneous mass of clinical material with varying clinical course, varying pathological picture and varying bacterial flora.

Etiology

As has been explained bronchopneumonia is not a clinical entity and therefore the etiology, as might be expected, is not uniform. Indeed the conditions causing this form of pulmonary inflammation are very diverse and complex. Bronchopneumonia does occur under circumstances which give it the appearance of an independent disease, but such occurrence is uncommon and for the most part it is secondary to some other disease or injury. Following such disease or injury, which somehow renders the lungs susceptible to infection, bacteria of different kinds enter the lung and set up an inflammatory reaction. When the bronchopneumonia is secondary to a specific infection, the bacterium causing it is seldom the same organism that causes the specific infection. Nor is it even in many instances a single variety of bacteria that invades the lung, for commonly two or three sorts grow together in the same lung. Bronchopneumonia is therefore in the anomalous position of being a quasi complication of many infectious diseases not due to the specific agent causing the primary infection, nor yet due itself to any single organism. The occurrence, the symptoms, the course of bronchopneumonia depend therefore in large measure upon the infection or trauma that precedes it, and also in part upon the particular organism that happens to be the infecting agent.

It might seem almost proper, were one disposed to do so, to lay all the emphasis in etiology upon the preceding infection or trauma and to slight as unimportant and accidental the particular organism that chances to be the infecting agent. Much might be said by a willing advocate in support of such a view. Certainly it is true that the clinical course of bronchopneumonia receives its characteristic marks as much, nay more, from the infection with which it is associated as it does from the infecting organism. For instance the bronchopneumonia complicating influenza runs a fairly typical clinical course, but the clinician is unable to predict with much more than a random chance of being correct what the bacteriological study of the lung will reveal. He cannot even predict invariably the anatomical features of the pneumonia, whether it be lobar or lobular. Furthermore an organism that will on one occasion produce a bronchopneumonia of the interstitial variety, may on another occasion produce a bronchopneumonia of the lobular variety, and on still another a frank lobar consolidation. Perhaps most important of all in this connection is the observation that locality plays an important part in deciding the organism that is active in bronchopneumonia. During the influenza epidemic of 1918, much confusion, mingled with some criticism and recrimination, was occasioned by the varying reports from different localities. Blame for this discordance was put upon errors of technic, but this seems hardly reasonable, particularly since some investigators obtained different results at different localities. And in some localities the predominant type of organism apparently changed. For instance MacCallum, who studied pathological material at Camp Lee in Virginia, Camp Dix in New Jersey, and at the Johns Hopkins Hospital in Baltimore, found the influenza bacillus predominantly at Camp Dix, only occasionally at Camp Lee, and not at all at Baltimore. At the two last named places the pneumococcus and the streptococcus predominated.

With due appreciation of these well-known facts and willingness to give them all the consideration they deserve, there is still room, I believe, to place important emphasis upon the infecting organism. Although a particular variety of pneumonia may be produced by a number of different organisms and a particular bacterium may cause different types of pneumonia, still it is true that a particular variety of pneumonia is usually due to a definite organism, or at least to one of two organisms, and that a given organism usually causes one variety of pneumonia. For instance, the pneumococcus is the important cause of lobar pneumonia; it often causes the lobular variety of bronchopneumonia; it practically never causes the interstitial variety; the hemolytic streptococcus is the important cause of the interstitial variety of bronchopneumonia; it very seldom causes lobar pneumonia; the influenza bacillus causes the lobular variety of bronchopneumonia and often also the interstitial variety, but it seldom causes lobar pneumonia. Lobar pneumonia and bronchopneumonia often exist side by side in the same lung, and the pneumococcus may be cultivated from the area of lobar consolidation, the streptococcus or influenza bacillus from the area of bronchopneumonia. The occurrence together of different organisms in bronchopneumonia may have an important influence upon the course of the disease as well as upon the pathological picture. One variety of organism may inaugurate a pneumonia, and then another variety may enter and supersede or modify the activity of the first invader. When three or four organisms are present, conditions become very complicated. Opie considers the role of the influenza bacillus in influenza pneumonia to be mainly of the nature of a preparatory influence. He found the influenza bacillus almost regularly in the bronchial secretion but seldom in the pneumonic exudate where the pneumococcus and streptococcus flourished. He looks upon the profound injury to the air passages, due he believes to the influenza bacillus, as the primary injury which allows other bacteria, notably the pneumococcus, the streptococcus and the staphylococcus to invade the lungs.

A third factor in the etiology of bronchopneumonia of sufficient importance to deserve notice is the mode of infection. I have so far spoken of bronchopneumonia as though it were always an infection by way of the respiratory passages. In most instances the infection is conveyed by this channel, but occasionally the infection is through the blood stream. Septic bronchopneumonia, as it is called, occurs almost exclusively with general sepsis, but occasionally it follows localized septic processes, particularly after operation. Finally, certain general features, such as age, exposure, debilitating diseases, are important contributory causes.

Therefore the etiology of bronchopneumonia may be considered from many different standpoints, and in order to present the matter satisfactorily, each of these standpoints must be considered separately. The accompaning table shows the factors in the outline:

I. Aerogenous Infections:
    1. Primary bronchopneumonia
    2. Secondary bronchopneumonia
        A. General predisposing causes
        B. Infections
            1. Non-specific respiratory infections
                Bronchitis
            2. Specific infections. Bronchopneumonia due to
                a. Specific organism
                    Tuberculosis
                    Plague
                    Diphtheria
                b. Non-specific organism
                    Measles
                    Influenza
                    Pertussis
                    Typhoid
        C. Trauma
            1. Trauma to chest wall
            2. Foreign particles aspirated
            3. Fluids aspirated
            4. Gases
II. Blood-Stream Infections
    1. General sepsis
    2. Local septic processes
III. Bacteriology
    1. Pneumococcus
    2. Streptococcus
    3. Influenza bacillus
    4. Staphylococcus
    5. Other organisms

I. Aerogenous Infections

1. Primary Bronchopneumonia

In adults primary bronchopneumonia is almost unknown, except in epidemic form; in children it occurs frequently during the first two years of life, rarely after the fourth year. In children the clinical symptoms are similar to those of lobar pneumonia, and the disease nearly always ends in recovery. The pneumococcus is the infecting organism usually recovered. The epidemic form of bronchopneumonia in adults is a highly contagious disease due to the streptococcus. The disease begins usually as a secondary form of bronchopneumonia and then becomes established as an independent disease of great virulence. In 1917 this form of pneumonia began in our cantonments as a complication of measles, but quickly gained an independent footing, spreading rapidly through the camps as a primary disease.

2. *Secondary Bronchopneumonia*

A. General Predisposing Causes.—Secondary bronchopneumonia is a common disease at all ages. It occurs with special frequency at the two extremes of life. In infants it is associated particularly with the specific infectious diseases; in old age particularly with bronchial catarrh and as a terminal event in chronic diseases. Debilitating influences of every kind and at every age predispose to bronchopneumonia.

B. Infections. 1. Non-Specific Respiratory Infections. Bronchitis.—The role that bronchitis or bronchial catarrh plays in the etiology of bronchopneumonia is sufficiently emphasized by the name. In contrast to lobar pneumonia, which hardly ever follows bronchitis, bronchitis nearly always precedes bronchopneumonia. In adults the bronchitis itself is usually secondary to some other condition, either a part of some specific infection, or a terminal event in some exhausting disease, or the result of trauma. In infants it may follow a primary bronchitis, but the bronchitis is usually associated with some specific infection. It is in old age that primary bronchitis plays its important role. However, even in old age debility or some chronic disease is usually present that lowers the patient's resistance, as we are accustomed to put it, and makes him an easy prey to bronchopneumonia when bronchitis develops. It is exceptional that a robust adult of any age develops bronchopneumonia after a primary bronchitis. Perhaps one exception should be named to this statement, the condition described clinically as capillary bronchitis. This disease has a fairly characteristic clinical picture. Unlike ordinary bronchitis, the inflammation is not restricted to the larger bronchi, but descends to their finest ramifications. Areas of bronchopneumonia are always associated with the bronchitis. Probably in this condition particularly does atelectasis play an important role. Much stress has been put upon atelectasis as an important pathogenetic factor in the development of bronchopneumonia.

2. Specific Infections.—The specific infections are the most important precursors of bronchopneumonia in childhood and early adult life. In infancy and childhood measles, pertussis, scarlet fever and diphtheria are the infections with which it is chiefly associated; in adult life measles and influenza; but it may occasionally be associated with any of the infectious diseases. In only three of the specific infections, namely, plague, tuberculosis and diphtheria, is the bronchopneumonia due to the bacterium causing the primary disease, and in all of these non-specific forms of bronchopneumonia also occur. I purposely omit influenza from this group because the influenza bacillus is not yet established definitely as the cause of influenza, and also because fewer of the bronchopneumonias are due to the influenza bacillus than to other organisms. In diphtheria and tuberculosis the bronchopneumonia is often an aspiration pneumonia due in the one instance to the inhalation of particles of diphtheritic membrane, in the other aspiration of blood laden with tubercle bacilli during a hemoptysis.

C. Trauma.—Under this heading I have put all injuries to the lungs, whether the injury be inflicted by a blow upon the chest or by the aspiration of foreign bodies or fluid or the inhalation of irritating gases. In many instances the aspirated material contains virulent organisms and the pulmonary injury and infection occur almost simultaneously; in other instances the aspirated material is sterile or contains only avirulent organisms, but the trauma makes the lung susceptible to invasion by virulent organisms entering through the bronchi.

While injury to the chest is not infrequently followed by lobar pneumonia, bronchopneumonia seldom follows such injury directly. If the injury be severe, associated conditions might easily lead to an aspiration bronchopneumonia.

The aspiration of foreign material into the lung is a common cause of bronchopneumonia and occurs under the most varied circumstances. It happens frequently in patients weakened and stuporous from a long illness, in comatose patients, after anesthesia, following submersion and so on. Aspiration pneumonia is a common sequel to operations about the nose and mouth, and to abdominal operations when normal expulsive efforts to clear the bronchi are suppressed. It follows the accidental inhalation of foreign bodies. It occurs frequently in association with other pulmonary infections as the result of aspirating infected material, as in bronchiectasis, carcinoma or empyema rupturing into the lung. Bronchial obstruction leading to retained secretion and atelectasis is usually followed by bronchopneumonia.

II. Blood-Stream Infections

Blood-stream infections occur in sepsis. Infected emboli lodge in the lungs and produce areas of bronchopneumonia which frequently suppurate. Less commonly local septic processes associated with phlebitis may produce areas of bronchopneumonia. These likewise usually suppurate.

III. Bacteriology

The pneumococcus, the streptococcus hemolyticus, the influenza bacillus, and the staphylococcus pyogenes aureus are the common causes of bronchopneumonia. Occasionally almost every known pathogenic organism is found, namely, the meningococcus, the plague bacillus, the diphtheria bacillus, Friedlander's bacillus, etc. The organisms do not cause specific lesions nor specific clinical symptoms, although each organism has a favorite type of anatomical and clinical reaction. The pneumococcus, for instance, causes lobar and lobular pneumonia, never interstitial pneumonia; the streptococcus causes chiefly interstitial pneumonia, seldom lobular pneumonia; the influenza bacillus causes lobular pneumonia more frequently than interstitial pneumonia, but frequently it causes an interstitial pneumonia indistinguishable anatomically from streptococcus interstitial pneumonia. Unless the disease occurs in epidemics the bacteriology cannot be predicted definitely from the anatomical lesion nor from the clinical course.

Pathological Anatomy

The pleura may be smooth and glistening, but if patches of consolidation are near the surface of the lung, they are covered with a thin fibrinous exudate. In certain types of bronchopneumonia seropurulent exudates into the pleural cavity commonly occur. The consolidated areas can usually be felt and on section they stand out more or less prominently as somewhat elevated patches differing in color from the surrounding lung tissue. In color they vary from red to gray, depending upon the proportion of blood and leukocytes in the exudate; in size from pin-head areas to confluent patches involving a whole lobe. When the areas are large the cut surface has not the uniform appearance of lobar pneumonia, areas of consolidation in different stages varying with areas of air containing lung. Owing to less fibrin in the exudate the surface is not so granular. The bronchi leading to the areas of consolidation are inflamed and their lumen contains purulent material. In some instances hypostatic congestion and atelectasis add further coloring to the varied picture. In fulminating infections patients may die before real consolidation occurs. The lungs are then deeply injected, the alveoli filled with blood and the bronchial mucosa shows hemorrhages and a hemorrhagic exudate. This condition has been named hemorrhagic pneumonitis.

Two anatomical types of bronchopneumonia have been described, interstitial pneumonia and lobular pneumonia. In *interstitial pneumonia* there is extreme infiltration of the bronchi leading to great thickening of their walls and distortion of the lumen, atelectasis of the portion of the lung supplied by the obstructed bronchus, the formation of small dense nodules about the terminal bronchioles, hemorrhagic exudate into the surrounding alveoli, and frequently a large pleural exudate, at first seropurulent, later more frankly purulent. Rapid organization of the inflammatory exudate occurs; the bronchial walls are thickened, the interlobular septa and the alveolar walls show a great increase in connective tissue, the lymphatics plugged with exudate become permanently occluded. No large areas of consolidation occur.

In *lobular pneumonia* the areas of consolidation are larger, there is no formation of dense peribronchial nodules, and the connective tissue reaction so characteristic of the interstitial variety is almost entirely absent. These two types of bronchopneumonia are often found side by side in the same lung.

Microscopically the exudate consists of leukocytes, red blood corpuscles and desquamated epithelial cells. The character of the predominating cell varies; usually polymorphonuclear neutrophiles predominate, but some exudates, particularly in interstitial pneumonia, are made up chiefly of small round cells. The amount of fibrin is always less than in lobar pneumonia and often is entirely absent.

Symptomatology

The symptomatology of bronchopneumonia is as varied as its etiology. Sometimes the symptoms are trivial and indefinite and the presence of bronchopneumonia may only be surmised; at other times they are dramatic and fulminating. It is impossible to convey a satisfactory impression of the symptoms and course of bronchopneumonia if it be treated as an independent disease. Its protean clinical manifestations can be viewed fruitfully only in the setting under which they naturally occur. However, there are a few general marks that distinguish it from lobar pneumonia.

The onset in contrast to lobar pneumonia is usually insidious. In patients with chronic disease a little fever, a slight cough, accelerated respiration, blood stained sputum, or the development of râles or a patch of bronchial breathing may call attention to the condition. Frequently it is discovered at autopsy when there were no particular symptoms to call attention to its presence during life. In severe bronchitis it may be impossible to tell definitely that bronchopneumonia is present unless a patch of consolidation can be outlined. We may safely assume that it is present with severe bronchitis of the small bronchioles even in the absence of definite physical signs. In infectious diseases, as in influenza and measles, the first event to call our attention to the presence of bronchopneumonia may be continued fever and other evidences of intoxication at a time when uncomplicated cases of the disease begin to improve; or there may be bloody sputum, localized râles, a patch of consolidation, polypnea or cyanosis. In interstitial pneumonia the severity of the constitutional symptoms and a pleural effusion may be the first evidence of bronchopneumonia.

The fever is very irregular. In terminal pneumonia it may be slight or absent. It is sometimes continuous, sometimes remittent. It is seldom as high as in lobar pneumonia, and the severity of the symptoms does not bear a constant relation to the height of the fever. Occasionally patients die of bronchopneumonia when the temperature is normal. The pulse and respiration are usually accelerated, but neither so constantly nor so strikingly as in lobar pneumonia. Cyanosis is often extreme and out of all proportion to the dyspnea.

The sputum is not characteristic. It is usually mucopurulent as in simple bronchitis. Sometimes it is very tenacious. When it is bloody the color is bright red; characteristic rusty sputum is seldom seen. Sometimes the sputum is hemorrhagic and profuse hemoptysis may occur.

Percussion and auscultation yield inconstant and varying results. At times no definite abnormal pulmonary signs can be discovered, even though the diagnosis may be made from the general symptoms. At other times suppressed breath sounds, persisting, localized râles or areas of dullness and tubular breathing may be found. The physical signs vary quickly from day to day, suggestive signs disappearing to reappear later or to be replaced by fresh signs in other locations. The lower lobes are nearly always the first to be involved, and the tendency to this localization is an important point in diagnosis. Termination of the disease by crisis is unusual; generally the symptoms disappear very gradually. The areas of consolidation clear up slowly and often remain for a long time after the constitutional symptoms have disappeared.

Primary bronchopneumonia in children has all of the clinical features of lobar pneumonia. It is caused by the pneumococcus, the symptoms are acute and severe, it ends nearly always in recovery. Aspiration bronchopneumonia has no characteristic symptoms. If the patient is comatose or otherwise very ill only trivial symptoms may direct attention to the condition. If the patient be robust and in good health all of the characteristic symptoms may develop. If the aspirated material be infected abscesses may form.

In terminal bronchopneumonia the symptoms are seldom striking. A little fever the last few days of life, or the development of cough are the common symptoms. Usually there is a little dullness over one or both lower lobes, suppressed breath sounds and moist râles, but sometimes outspoken signs of consolidation develop, while at other times no abnormal physical signs can be discovered. So commonly does bronchopneumonia occur as a terminal event in chronic renal and cardiac disease that clinicians often predict its presence even in the absence of definite symptoms or signs.

Bronchopneumonia Associated with the Infectious Diseases. 1. Influenza.—In some severe cases pneumonia seems to begin with the onset of the illness. More commonly it develops from the third to the fifth day, sometimes later. As a rule, the symptoms come on insidiously. In uncomplicated cases of influenza the temperature begins to fall on the third, fourth, or fifth day. Persisting or increasing fever at this period at once awakens the suspicion that pneumonia is developing. At the same time the constitutional symptoms instead of improving grow worse, the patient becomes more deeply intoxicated, cough and sputum increase, the respirations become somewhat accelerated. Bloody sputum which is frequently an early symptom always indicates pneumonia. At this period the physical examination may disclose no definite signs, or there may be only a few localized fine râles or suppressed breath sounds. Later patches of consolidation become evident, which may gradually spread and involve large areas of the lung. At any stage the symptoms may subside either abruptly by crisis or more commonly by lysis. The physical signs may persist for a long time, and are often demonstrable by the X-ray months after the patient has recovered. If the process spreads the patient becomes more and more deeply intoxicated. Cyanosis is often extreme. The sputum becomes profuse and bloody. Cough is harrassing and uncontrollable. The patient usually becomes delirious, but not infrequently clear consciousness is maintained almost to the moment of death. In contrast to the cyanosis, the dyspnea and the profound prostration the heart action may remain astonishingly slow and vigorous. The pulse may be slow and of excellent quality a few minutes before death. Pulmonary edema is common and extreme, frothy serum sometimes literally pouring from the mouth. The leukopenia characteristic of influenza persists even after pneumonia has developed. Empyema is rare and abscess and gangrene occur less frequently than in lobar pneumonia. Subcutaneous emphysema is remarkably common. Jaundice frequently comes on and is an ill omen. The disease is extremely fatal; from twenty-five to forty per cent. of those affected die.

2. *Measles.*—Bronchopneumonia may develop at any stage of the disease. It comes on most frequently as the eruption begins to fade. The persistence of high fever, instead of its defervescence on the fifth or sixth day, particularly if the cough becomes aggravated, is very suggestive of bronchopneumonia. Bronchopneumonia coming on at the height of the eruption is often accompanied by a rapid fading of the eruption, an observation justifying the great danger the laity associate with the eruption striking inward. The physical signs vary as they do in influenza bronchopneumonia. The illness is usually accompanied by severe symptoms of intoxication. Two special forms of bronchopneumonia occur with measles. (a) Following measles there is a tendency for tuberculous lesions to flare up and extend. A disseminated tuberculous process in the lungs may simulate bronchopneumonia. The duration of the symptoms will suggest the tuberculous nature of the lesion but since bronchopneumonia may be prolonged into a subacute form, the distinction is often difficult. (b) Epidemic streptococcus bronchopneumonia is often associated with epidemics of measles. There are characteristic features to this type of pneumonia, both clinically and pathologically.

3. *Pertussis.*—Bronchopneumonia is a frequent complication of pertussis in infants, less common after the second year and relatively uncommon

after the fourth year. It occurs usually during the period when the paroxysms are most severe. The clinical course of the disease is similar to bronchopneumonia with measles. Subacute forms of the disease are frequent, often simulating tuberculosis. They sometimes terminate in bronchiectasis. Interstitial streptococcus bronchopneumonia is a common type just as it is with measles.

4. *Diphtheria.*—In diphtheria bronchopneumonia may be due to an extension of the diphtheritic membrane to the bronchi. This is a severe and almost uniformly fatal form of the disease. More commonly the bronchopneumonia follows the aspiration of infected material into the bronchi, but the pulmonary inflammation is not caused by the diphtheria bacillus. Fever, dyspnea and cough are the usual symptoms. The physical signs are the same as those described for influenza bronchopneumonia. In diphtheria streptococcus bronchopneumonia is common.

Epidemic Streptococcus Bronchopneumonia

For centuries epidemics of pneumonia have been described which in the light of later experiences we may with reasonable assurance place in this class. These epidemics have for the most part occurred when large numbers of recruits have been brought together, and they have nearly always accompanied and followed epidemics of the exanthemata, particularly measles. A formidable epidemic started in Canada in 1812 and spread over the United States. During the Civil War measles and pneumonia were common in the Armies, although the disease did not attract particular notice, being overshadowed by the ravages of typhoid and dysentery. In the winter of 1917 the cantonments throughout this country were visited by an extensive outbreak of measles followed by an epidemic of virulent streptococcus pneumonia. This malignant and fatal form of pneumonia has occurred also in smaller and more localized epidemics amongst the civil population. Finkler in 1888 reported several small outbreaks of the disease, and described the severity of the clinical manifestations, the pathological characteristics of the lung changes and the causal relation of the streptococcus. The pathological characteristics of the severe bronchopneumonias following measles, diphtheria and pertussis were first clearly described by Bartels in 1861. He notes all the important characteristics of the lesions we now speak of as interstitial bronchopneumonia. Finkler and Durck emphasized the importance of the cause of the pneumonia.

The epidemic in the United States Army Camps in 1917 followed immediately upon a widespread epidemic of measles. All of the early instances came on as a complication of measles, but once the pneumonia had become prevalent it began to attack healthy soliders who had not had measles. The infection was most malignant. It was characterized by symptoms of extreme intoxication, intense dyspnea and cyanosis, with a remarkable tendency to pleural exudation. In many instances the pulmonary lesions were completely obscured by a massive pleural effusion which began a few hours after the onset of the illness. The effusion consisted at first of turbid serum containing innumerable streptococci which gradually became frankly purulent. The pulmonary lesions, thoroughly described by MacCallum, were characteristic of interstitial bronchopneumonia, often associated with areas of lobar or lobular consolidation. The outstanding characteristic of the epidemic was the prevalence and extent of pleural effusions, a condition entirely missed during the influenza epidemic the following year. Almost regularly the streptococcus hemolyticus was cultivated from the lung, although often the pneumococcus and other organisms were found associated with it.

Treatment of Bronchopneumonia

The only sure prevention of bronchopneumonia is the prevention of the specific infections with which it is so frequently associated. The control of diphtheria is an example of what may be done in this direction. In drowsy and comatose patients care should be exercised in feeding. Patients with acute respiratory infections should not be given anesthetics unless there is urgent need of operation. During the recent epidemic of influenza much interest was aroused in the administration of vaccines. The purpose was not to prevent the onset of influenza but to prevent the development of pneumonia. Killed mixed cultures of the organisms chiefly implicated in the pneumonia, namely, the pneumococcus, the streptococcus, the influenza bacillus and the staphylococcus were used. Opinions vary widely about the benefit derived from such preventive inoculation, and their value is far from demonstrated. Since it has been shown that numerous strains of each type of organism exist and that each strain has distinct immunological properties, it seems altogether unlikely that the injection of stock vaccines will produce any satisfactory immunity. Similar vaccines have been used in treatment. Their use is unscientific and of no appreciable value. Serum of recovered patients has been used without demonstrable benefit. The injection of non-specific protein is also of doubtful value.

In the absence of any remedial agent for bronchopneumonia the treatment must be confined to the general management of the situation. The details cannot and need not be dwelt upon. Absolute quiet, both physical and mental, must be enforced. Plenty of fresh air and good nursing are important. The diet must be planned to suit the patient; semisolid foods may be given if the patient is in good condition. Water should be freely given. The bowels should be regulated with laxatives and enemata, but purging is inadvisable. Sponges may be given if the fever be high, or for the nervous symptoms. If the pain be severe the side may be strapped, or better still a suitable swathe or jacket worn. Digitalis may be given to prepare for the occasional onset of auricular fibrillation or flutter, otherwise digitalis has not the least influence upon the disease. Caffein, strychnin and camphor are popular so-called stimulants; but it is doubtful if they do the least bit of good and given in too large doses they may do harm. The one drug that has definite value is opium. It should be used with discretion, but within the limits of discretion, freely. Codein, heroin and morphin are the most useful preparations.

Abscess and Gangrene

There is an advantage in departing from the older custom of treating abscess and gangrene as separate pulmonary diseases and grouping the two conditions together under pulmonary suppuration. Both clinically and pathologically they are so closely related that there is no sharp distinction between them, and to describe them separately necessitates endless repetition and the use of artificial and needless distinctions. They have the same causes, they produce similar symptoms, and the treatment of both is identical. Abscess frequently, if not always, precedes gangrene, and the two conditions often exist side by side.

Abscess and gangrene may be divided into two main groups: (1) those due to aspiration of foreign bodies and infected material into the bronchi, and (2) the postpneumonic. These two groups will include at least ninety-five per cent. of the cases. Less frequent causes are bronchiectasis, which is commonly followed by gangrene, septic emboli, the rupture of contiguous areas of suppuration into the lung, and a host of chronic pulmonary diseases in which secondary infection occurs. In the last named group may be mentioned cancer, sarcoma, dermoid cysts, tuberculosis, syphilis, echinococcus cysts, fungus infections, etc. Empyemata not infrequently rupture into the lung, as do also abscesses in the liver and subphrenic abscesses. Perforation of the esophagus, vertebral caries, and suppurating bronchial glands may also give rise to abscess and gangrene. Pulmonary infarcts occasionally become infected and produce abscesses. Infection anywhere in the body may cause embolic pulmonary abscesses from infected venous thrombi. They are usually multiple and play a secondary part in the clinical features of the primary infection.

Aspiration abscesses are particularly common after operations about the oral cavity. During the past few years great prominence has been given to the frequent occurrence of lung abscess following removal of the tonsils. In a series of 100 consecutive cases published by Wessler twenty-one followed tonsillectomy. Less common causes are the inhalation of foreign bodies, especially in young children, the inhalation of infected material or food particles in unconscious states, submersion, trauma, etc.

Postpneumonic abscess and gangrene is rare clinically in lobar pneumonia. Most of the abscesses recognized clinically follow rupture into the lung of an empyema. Aufrecht in 1,501 cases of lobar pneumonia observed no instance of gangrene. At autopsy abscesses of various size are frequently discovered, suggesting that they are often recovered from and escape clinical detection. Bronchopneumonia is more frequently followed by abscess and gangrene than lobar pneumonia. It is thought to be particularly frequent after influenzal pneumonia, but the experiences of our recent epidemic do not bear out this impression. It is probable that bronchopneumonia is more commonly a forerunner of abscess than is generally recognized, for patches of bronchopneumonia no doubt precede abscess formation in all cases of aspiration abscess.

Pathology

When infected material is aspirated into a bronchus, the material with the inflammatory exudate about it plugs the bronchus. The occlusion of the bronchus, together with the infection, produces a dilated bronchial sac filled with infected exudate. The infection rapidly spreads to the surrounding lung and the alveoli become filled with leukocytes and fibrin. This inflammatory exudate undergoes gangrenous liquefaction and a small cavity is formed. The pulmonary infiltration displays from the beginning a strong tendency to organize, and the production of scar tissue may compress neighboring bronchi and numerous small abscesses may thus be formed. These small abscesses frequently coalesce, producing a large irregular cavity. The organisms concerned in this process have not been satisfactorily studied. Buday has described a number of different bacteria, laying particular stress upon a fusiform bacillus and a spirillum as the specific organisms. Wessler emphasizes the appearance of the evidence of gangrene, namely, foul sputum or breath regularly on the fourteenth day after the aspiration of the infected material, and this uniform interval leads him to assume the action of a specific agent with a uniform incubation period. He assumes that the organism is anerobic.

The occurrence of an abscess in an area of preceding pneumonic consolidation cannot be so clearly followed. It usually comes on insidiously, and perhaps the first stage is organization of the exudate followed by bronchial obstruction and the formation of cylindrical bronchiectases. In these cases also the interval is usually two weeks before the sputum or breath acquires the characteristic odor.

The gross appearance of pulmonary abscesses depends upon their etiology and the stage of development. Acute abscesses appear as gray, yellowish, or red areas of softening from which pus can be expressed. When cavities form they may be single or multiple or communicating. They vary greatly in size. In an early stage the walls are ragged and soft and not sharply marked off from the surrounding tissue. Old abscess cavities may be smooth and surrounded by an area of dense fibrosis. Bands containing branches of the pulmonary artery and thrombosed veins often run through the cavity. The lung tissue about the abscess is infiltrated and fibrosed. There is always marked induration about the abscess and sometimes widespread and diffuse induration of a lobe or the whole lung. Abscesses frequently lie beneath the pleura and the pleura is often involved. The pleurisy may be dry or there may be a purulent or gangrenous pleural exudate.

Laennec divided gangrene into two classes, diffuse and circumscribed, and this division is still adhered to. In the diffuse variety a whole lobe or a still greater area of the lung may be involved with no sharp demarcation from the surrounding unaffected area. The gangrenous area presents a greenish gray or brown color and is soft and pulpous. In the circumscribed variety one or more areas of varying size exist, which are at first dry and greenish gray in color, later moist, soft, greenish brown or black in color, with central softening and cavity formation. These areas are limited by a zone of pulmonary infiltration and edema, and in chronic cases by a pyogenic membrane.

Pulmonary abscesses may be found in any of the lobes, although the middle lobe is seldom involved. Aspiration abscesses, particularly postoperative, are more frequent in the upper lobes than in the lower, about two to one; postpneumonic abscesses occur more frequently in the lower lobes than in the upper, about two to one. They are more commonly situated near the pleura than deep in the lung substance.

Symptoms

The symptoms and the clinical course of lung abscess depend somewhat upon the cause. They are more distinctive and more characteristic in aspiration abscess than in other forms, because in the former group the condition has the characters of an independent and primary disease. Occasionally an abscess will develop without known provocation, as in one instance I have seen in which it came on after a long automobile drive, probably due to the aspiration of some small foreign body of which the patient was unconscious. A day or two after a tonsil operation or after exposure the patient develops fever and cough. The temperature persists, the cough becomes more and more severe, and varying amounts of mucopurulent sputum are raised. The leukocytes are moderately increased in number, the polymorphonuclears predominating. Physical signs may reveal no pulmonary abnormality or there may be evidence of local infiltration and consolidation.

The diagnosis of bronchopneumonia is usually made. At the end of a week the temperature becomes irregular, the cough is more severe and larger amounts of mucopurulent sputum are expectorated. About the fourteenth day the sputum usually acquires a characteristic, fetid odor, and the diagnosis of abscess can then be readily made. During the third or fourth week the symptoms as a rule begin to change somewhat. The temperature becomes frankly septic in type and displays variations in proportion to other symptoms. Cough may become less annoying and large amounts of sputum may be brought up at one time. At times the sputum has a disagreeable odor, at other times none. Often these symptoms go along in a recurring sequence. The patient will expectorate a large amount of fetid sputum, the temperature will drop, cough will diminish and the patient will experience sensations of relief and relative well-being. The temperature may remain at nearly a normal level for a day or two and give rise to the hope that recovery is on the way. Then gradually the temperature mounts again, the symptoms of intoxication return, cough becomes harrassing, but only a little mucopurulent sputum comes up, until after a number of days suddenly a large amount of fetid sputum is expectorated and temporary improvement again begins. During this period the sputum is often bloody and occasionally frank hemoptysis occurs, although large hemorrhages are nearly always restricted to later stages of the disease.

During the second month of symptoms many abscesses gradually heal. The symptoms slowly recede and finally the temperature remains normal, cough and sputum disappear and the general health is rapidly restored. Sometimes an abscess will rupture into the pleura and will heal when drainage of the pleural cavity is established. Sometimes an abscess produces widespread pulmonary suppuration and gangrene and may be rapidly fatal.

Abscesses that do not heal within two or three months enter a chronic stage and hope of spontaneous cure must then be abandoned. When pulmonary induration has reached an advanced stage complete obliteration of the abscess cavity is not likely to occur. The patients from then on have symptoms like those with bronchiectatic dilatation. They have cough with profuse expectoration, which is sometimes restricted to certain times of the day. For instance they may empty the cavity or cavities two or three times a day and be free from cough during the intervals. Unfortunately even such a relatively satisfactory state of affairs seldom exists. The sputum is often transiently or permanently so foul that the patients are social outcasts; they have recurring attacks of fever that undermine the general health; hemorrhages are frequent; and they are constantly in danger of the more serious symptoms of rapidly spreading pulmonary infection. As a rule they live a few ungrateful and unwelcome years, and exhausted by their disease, finally die of bronchopneumonia.

The symptoms of abscess following lobar pneumonia are not nearly so distinctive. At the termination of the acute symptoms of the disease, fever persists and the consolidation fails to resolve. Empyema, induration, abscess and tuberculosis are suspected. The fever is usually irregular there is increasing cough and mucopurulent sputum and the leukocyte count remains elevated. The diagnosis is definitely made when the sputum acquires the characteristic odor or when large amounts of purulent sputum are expectorated at one time. The evacuation of the abscess may be followed by recovery or the abscess may go on to the chronic stage already described.

As has been pointed out localized gangrene nearly always goes hand in hand with abscess formation. It gives the characteristic odor to the sputum. When gangrene oversteps these local bounds and becomes widespread more serious symptoms supervene. The temperature is higher and the evidence of more severe intoxication is apparent, the patients lose flesh and strength more rapidly and the disease is more often quickly fatal. The sputum is usually more fluid than in abscess, of a greenish, dirty brown or prune-juice color. The fetid odor is intense and may penetrate a whole house.

The physical signs of abscess are not at all distinctive. In the early stages no, or only slight, abnormalities may be discovered. Later the signs are those of local consolidation or of cavity. It may well be emphasized again that abscesses frequently occur in the upper lobe.

The characteristic features of the sputum are the odor and the occurrence of shreds of pulmonary tissue. Its appearance is by no means uniform. It may be thin and purulent, or tenacious, and varies in color from a pale green to brown and almost black, depending largely upon the amount of blood and the changes the blood pigment has undergone. On standing it usually separates into three layers, on top masses of discolored frothy sputum dipping down in strands into the middle layer of cloudy watery fluid and a heavy sediment of pus at the bottom. Shreds of pulmonary tissue may be large enough to be recognized by the unaided eye. When the sputum is allowed to stand these and smaller masses fall to the bottom, and they may be identified by the demonstration of elastic fibers. Dittrich's plugs may also be found. These are soft putty-like masses, made up of bacteria, fatty acids, free fat and debris, of a most disagreeable odor.

Roentgenological examinations are of the greatest help in the diagnosis of pulmonary abscess and are indispensable in the treatment of the condition. An abscess casts no characteristic shadow by which it may be recognized, but its location and the condition of the surrounding lung tissue will often help to distinguish it from empyema and tuberculosis. Not infrequently abscess is diagnosed clinically, and the X-ray will demonstrate the presence of an unsuspected foreign body in a bronchus. This occurs over and over again in young children. If operative treatment is indicated the

X-ray will tell better than any other method of examination the location of the abscess, whether it is single or multiple, and the best route of approach.

Pulmonary hemorrhage and brain abscess are the two most common complications of lung abscess. Fatal hemorrhage usually occurs only in chronic abscess when it is due to the rupture of an aneurysm of a branch of the pulmonary artery traversing a cavity. In gangrene fatal hemorrhage may occur at an earlier stage. Although general sepsis is uncommon, brain abscesses are often multiple. Clubbing of the fingers often occurs early and rapidly in lung abscess.

Treatment

A large number of lung abscesses recover spontaneously. Treatment in the early stages can be only supporting and symptomatic. The cough particularly must be controlled by sedatives. In children an X-ray examination or a bronchoscopic examination should always be made to exclude foreign bodies. It is to be remembered that some foreign bodies do not appear in an X-ray. Such examinations cannot be too strongly urged. In later stages of the disease proper care of the general health is important. Patients' symptoms can often be relieved and their general condition improved by practising the assumption of postures that drain the lung. Garvin has emphasized the value of this procedure in bronchiectasis. The odor of the sputum can often be destroyed by posture drainage and various inhalations. The creosote cabinet is sometimes successful. Oil of turpentine, oil of eucalyptus or myrtol internally may effect the same result. The latter remedy may cause unpleasant symptoms of intoxication.

The only hope of permanent relief for patients that fail to clear up spontaneously is surgical intervention. There are many problems connected with the surgery of lung abscess that need further investigation and inquiry, but with the rapid improvement being made in lung surgery results are sure to become more consistently successful. A fairly large proportion of lung abscesses, especially the aspiration variety, heal spontaneously, therefore one hesitates to advise operation prematurely. On the other hand, the longer the operation is postponed the less chance is there of complete and satisfactory recovery. When induration is advanced simple drainage of the abscess may give great relief, but the symptoms do not completely disappear. Cavities or bronchiectatic dilatations remain and the patients continue to have cough and expectoration. In acute cases it is very difficult to decide just when operation should be performed. No general rules can be given but each case must be rigorously studied from every angle before the decision is made. In one instance in which I urged operation my advice was not accepted and the patient made a rapid and complete recovery. In long-standing cases a choice must be made between accepting the relief afforded by drainage, which is relatively safe as far as life is concerned, and the attempt to procure a radical cure by difficult and dangerous lobectomy.

Some observers have used artificial pneumothorax and report satisfactory results. This procedure could not be of any value in chronic cases with extensive induration. Some observers report distinctly harmful effects.

Chronic Inflammatory Conditions in the Lungs

Under this heading is collected a heterogeneous group of diseases, or rather conditions, varying in etiology, in pathological anatomy and in clinical symptoms. A portion of the cases represents a later stage of some acute process and are best treated under the heading of the diseases they follow. Another portion represents, strictly speaking, no inflammatory condition, but the scarring and induration that follow inflammation. However, still another portion, although a small portion, represents an apparently independent disease; the process starts as a low grade infection and persists for years without definite healing. In treating chronic inflammatory pulmonary diseases they are best divided into (1) pulmonary cirrhosis, induration or fibrosis, (2) secondary chronic inflammatory diseases, (3) primary chronic inflammatory diseases.

Pulmonary cirrhosis or induration follows the healing of any chronic pulmonary inflammation. The common causes of induration of large areas of the lungs are unresolved pneumonia, pulmonary tuberculosis and extensive pleurisy. Syphilis and pneumonoconiosis are less common but important causes. Smaller areas may follow the most diverse pulmonary lesions. Small areas of induration give no important symptoms; larger areas lead to retraction of the chest wall, diminished mobility, dislocation of the mediastinum, dullness and diminished or blowing breath sounds. Bronchiectasis commonly occurs in association with cirrhosis and explains the cough and sputum that are frequently present. The other important effect of induration, especially when it is diffuse, is the production of emphysema, and by interference with the pulmonary circulation, hypertrophy and dilatation of the right side of the heart. When the condition is extensive dyspnea and cyanosis are present.

Secondary chronic inflammatory disease of the lungs, or as it is often called chronic pneumonia, is usually a step on the way to cirrhosis. Unresolved lobar pneumonia is the commonest cause. There is no sharp distinction between chronic pneumonia and induration. Some authors restrict the term chronic pneumonia to instances in which symptoms, particularly fever, persist. Bronchopneumonia may be followed by a similar train of events. It is important to emphasize that the term chronic pneumonia covers a host of diagnostic errors. Frequently the original disease which has failed to resolve was not a genuine pneumonia. Tuberculosis is often the cause of the condition.

Primary chronic inflammatory disease of the lungs is an unusual but in many respects an important condition. On account of the similarity of its symptoms with the symptoms of pulmonary tuberculosis the condition has been described frequently as chronic non-tuberculous pulmonary disease. The onset may be gradual or abrupt. In most instances it comes on insidiously with symptoms that cannot be distinguished from those of an ordinary cold; less frequently it begins with symptoms suggesting a mild bronchopneumonia. Instead of the symptoms subsiding promptly, as they do in an ordinary acute respiratory infection, they persist indefinitely. Patients have been under observation for ten years with little change in their symptoms. There is usually fever and cough and expectoration which vary in intensity from time to time. Blood spitting is common and sometimes there is profuse hemoptysis. In spite of the prolonged fever the patients are usually in good general condition and complain only of the cough and sputum. Examination reveals nearly always lower lobe lesions, slight dullness, harsh or diminished breath sounds and numerous moist râles. The symptoms vary in intensity from time to time, sometimes disappearing almost completely. Attacks of pleurisy are common. One patient after having been under observation for six years died of a rapidly fatal empyema. At autopsy the bronchi in both lower lobes were dilated and filled with purulent material. About the dilated bronchi were scattered areas of bronchopneumonia. Sputum cultures show pneumococcus, influenza bacillus and streptococcus, often in pure culture. There is no satisfactory treatment for the condition. The symptoms may be allayed by proper remedies. General measures directed to building up the patient's condition are the most important. Vaccines have disappointed me.

Specific Infections*

Syphilis

Syphilis of the lungs is occasionally diagnosed clinically; it is seldom recognized with certainty at autopsy. An indurative pulmonary lesion, particularly when it is situated in the lower or middle lobes, occurring in an individual who has a syphilitic infection which clears up promptly upon the vigorous administration of antisyphilitic remedies, is assumed to be syphilis of the lung. However, anatomically syphilitic lesions are difficult to distinguish from tuberculosis and from other forms of pulmonary induration, and no doubt much of what was formerly described as syphilitic phthisis was in reality tuberculosis. In contrast to tuberculosis, which is common in the lungs but rare in the upper respiratory passages, syphilis is common above and rare in the lungs. It not infrequently causes ulceration in the trachea, and the point of bifurcation is a favorite location. As the lesion heals contraction occurs and one of the main bronchi may become occluded. As a result there develop extensive bronchiectasis and fibrosis of the lung.

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* Tuberculosis is discussed in Vol. V, Chapter XXII.

Pathology.—The most characteristic lesions of syphilis of the lungs occur in the congenital form. These lesions consist of gummatous nodules, extensive induration and the desquamative process spoken of as "white pneumonia". They often occur side by side in the same lung. Definite localized gummata are rarely found, the condition usually consists of induration and desquamation of alveolar cells. The lungs are large and firm and white. Microscopically the alveolar epithelium is cubical in form and the alveoli are filled with desquamated epithelial cells and a few leukocytes and mononuclear cells. The alveolar septa are tremendously thickened and there is marked proliferation of the connective tissue about the bronchi and blood vessels. The blood vessel walls are greatly thickened and many are occluded. Children with such extensive lesions are born dead or die shortly after birth. When the lesions are less marked the children may live, and it has been suggested that syphilis may be the underlying cause of extensive pulmonary induration and bronchiectasis which occasionally develops insidiously in young children. Late forms of congenital pulmonary syphilis are described that come on at puberty or later. These instances have the characters of the acquired form.

Acquired syphilis of the lungs may occur as gummata, as diffuse or local induration, and perhaps as a gelatinous pneumonia. The occurrence of syphilitic gelatinous pneumonia is much discussed, but it has neither clinical nor anatomical features by which it may definitely be recognized. Gummatous lesions seldom occur apart from indurative lesions. They vary in size from tiny nodules to tumors as large as an egg. These nodules are usually situated near the hilus and in the lower lobes and are always associated with marked fibrous tissue proliferation. In the course of time they degenerate and caseate and are finally replaced by dense scar tissue. In this way large bands of connective tissue may run throughout the lung, and by compressing the bronchi, lead gradually to a diffuse bronchiectasis. The walls of the blood vessels participate in a striking degree in the connective tissue proliferation and many of the vessels become obliterated. When this process is extensive and diffuse the pulmonary circulation may be seriously interfered with and the right side of the heart gradually becomes enlarged. This extensive pulmonary fibrosis cannot be recognized definitely as syphilitic. The diagnosis depends upon the absence of the evidence of tuberculosis, the occurrence of syphilitic lesions elsewhere and occasionally upon the demonstration of the spirochete.

Symptoms.—When the congenital form is well developed the children are born dead or die shortly after birth. So-called late congenital forms of pulmonary syphilis do not differ from the acquired form.

During the secondary manifestations of the syphilitic infection bronchial catarrh with cough and expectoration are frequently present. These symptoms are occasioned by the presence of the syphilitic efflorescence upon the bronchial mucous membrane. The symptoms disappear as the eruption clears up.

In the late syphilitic pulmonary affections there are no characteristic symptoms. The disease is assumed to be present when tuberculosis is excluded and when the patient has elsewhere the signs of a syphilitic infection or a positive Wassermann test. The correctness of the diagnosis is then tested by the effects of treatment. There are, however, certain features of the pulmonary lesion that may suggest their syphilitic nature. The lesion is much more commonly situated in the middle and lower parts of the lungs, leaving the apices free. This is in striking contrast to chronic tuberculous processes which almost uniformly involve the apices. The lesions are characterized also by marked dullness with diminution in the intensity of the breath sounds and the paucity of râles. The presence of fever over a long period of time with little deterioration of the general health is another suggestive symptom. Whenever a patient has a chronic indurative pulmonary lesion and tubercle bacilli are constantly absent from the sputum syphilis should be suspected. A careful investigation for other evidence of syphilitic infection, the Wassermann test and the results of treatment, will decide the diagnosis. The frequent association of tuberculosis and syphilis in the same patient should be emphasized. Syphilis of the lungs occurs usually in two forms, a subacute form simulating ulcerative phthisis and a chronic form coming on insidiously as a pulmonary fibrosis. The clinical symptoms of the former type are those of pulmonary tuberculosis. There is cough, dyspnea, cyanosis, fever, loss of weight and strength. As has been noted the location and character of the lesion may suggest at once a non-tuberculous infiltration. Fever is usually less marked than in tuberculosis and the wasting less striking. On the other hand dyspnea is more prominent. Hemoptysis occurs but apparently not so frequently as in tuberculosis. When fever is present it yields almost at once to iodides.

In the chronic indurative type of the disease the symptoms resemble those of fibroid phthisis. The patients have cough and expectoration, and as bronchiectasis usually develops, they may have the symptoms and signs of cavity. The sputum is sometimes putrid. There may be an irregular, septic temperature and the patients may become markedly emaciated. In these chronic cases the pleura is often involved and great thickening of the pleura may accentuate the pulmonary sclerosis.

The sclerosis of syphilitic disease always involves the branches of the pulmonary artery to a marked degree. In rare instances the pulmonary involvement is relatively insignificant and the disease consists primarily of a diffuse and generalized sclerosis of the pulmonary arterioles. This condition gives no physical signs and usually passes unrecognized until cardiac symptoms develop. Even then the true state of affairs is usually overlooked and the myocardial insufficiency is ascribed to disease of the heart muscle. At autopsy the tremendous hypertrophy and dilatation of the right heart and the extensive disease of the pulmonary arteries explain the sequence of events. Warthin has described a remarkable case diagnosed mediastinal tumor and later Osler-Vaquez disease. The clinical course was characterized by attacks of angina hypercyanotica, cyanosis, increasing weakness, drowsiness, edema, asthma, dyspnea, enlargement of spleen and liver, multiple telangiectasias and constant erythremia. The autopsy revealed extreme atherosclerosis of the pulmonary artery and all its branches, extreme dilatation of the right heart, fibrosis and emphysema of the lungs, extreme angiectasia of the entire vascular system, enlargement of the liver and spleen and hyperplasia of the bone marrow. Microscopically the changes in the pulmonary arteries were typically syphilitic. Warthin regards the syphilitic pulmonary arteritis as the first link in the chain of symptoms, and points out that the symptoms correspond to those described in Spanish-American literature as Ayerza's disease or cardiacos negros.

Treatment.—There is nothing peculiar about the treatment of pulmonary syphilis; it is the same as the treatment of the disease elsewhere. The only point that needs emphasis is the importance of making the diagnosis before extensive fibrosis has occurred. Large gummata, large areas of infiltration and even beginning fibrosis may resolve under energetic treatment. Even cavities may heal. However, when fibrosis has become extensive and bronchiectatic cavities have formed, the condition can no longer be cured, and in spite of treatment symptoms persist and the patients remain in danger of all the hazards these conditions entail.

Pulmonary Actinomycosis

There is still a good deal of confusion respecting the classification of actinomyces. It is closely related to streptothrix, and some investigators combine the two organisms under the genus trichomycetes, a suborder of hyphomycetes. Others feel that the organism has sufficiently distinctive characters to warrant making it a special genus. The biology of the organism has been carefully worked out by Wright. (See Vol. V, Chap. XXIV.)

Pathology.—In tissues the organism forms masses of tangled branching mycelium of irregular rounded shape, grayish or yellowish in color. They vary in size from minute particles to masses from one to two mm. in diameter.

The larger masses are visible to the naked eye and are the characteristic so-called sulphur granules. The central portion of the mass is made up of dense, closely packed mycelium from which branches project radially. These branches are capped by a club-shaped or bulbous covering of homogeneous refractive material. On section the central portion shows a mass of tangled fibers, cells and amorphous debris about which there is a dense network of interlacing filaments and at the periphery a scalloped margin of clubs arranged radially. These clubs are not always present and when they are absent the parasite cannot be definitely identified. They occur only in the granules from pathological lesions and are not formed when the fungus is grown on artificial media. They probably represent a protective reaction against the influence of the tissue cells and juices.

The organism stains by Gram's method and can be cultivated anerobically upon a glucose agar medium.

It is generally stated that actinomycosis is introduced into the human body by straws or bits of grain, but this view is based upon the erroneous assumption that actinomyces is identical with certain similar and widely distributed fungi. As a matter of fact, genuine actinomyces have never been found outside of the body of man or certain animals, and the conviction is rapidly growing that infection occurs from parasites that normally inhabit the mouth and the intestinal tract. Foreign bodies act as provocative agents, not as carriers of infection.

Having settled in the tissues the organism rapidly causes necrosis of the surrounding cells. A mass of leukocytes is poured in and liquefaction of the necrotic tissue occurs. The destructive process proceeds very slowly and is gradually surrounded by a dense mass of connective tissue, the inner zone of which is composed of large mononuclear, phagocytic cells which undergo fatty degeneration, giving this layer an opaque yellow color. Giant cells are seldom found. The pus in the central necrotic area contains numerous branching organisms and the sulphur granules. This process of inassion, necrosis, liquefaction and fibrosis slowly but relentlessly proceeds. Every tissue that stands in the way of the invading organism is penetrated and destroyed, and this destructive process is accompanied by the most extreme connective tissue formation. Large, tumor-like masses of scar tissue are formed surrounding cavities filled with pus that connect with one another by tortuous sinuses.

The disease is usually situated in the lower lobes and begins as a rule about the smaller bronchi. The cavities usually connect with bronchi and the organisms are frequently ejected in the sputa. The process usually reaches the pleura, causing tremendous pleural thickening, and from there, as a rule, pierces the chest wall, producing one or more intractable sinuses, which discharge purulent material in which the characteristic granules may be found. The tremendous scar tissue formation leads gradually to extreme contraction of the affected side. The disease spreads in spite of every obstacle and often invades the heart, the mediastinum, erodes the vertebrae, traverses the diaphragm and attacks the abdominal organs. In late stages metastases occur in the spleen, kidneys, brain and other organs.

Symptoms.—The most characteristic symptoms of pulmonary actinomycosis are the marked contraction of the side, perforation of the chest wall and the occurrence of sulphur granules in the sputum or the secretion from a sinus. The latter symptom alone is distinctive. In the early stages the patients have cough and sputum without characteristic physical signs, usually only a small number of râles is heard. The diagnosis can only be made by finding the organism in the sputum. Later pleural pain becomes prominent, cough and sputum increase, dyspnea becomes more and more marked and fever and emaciation occur. At this stage there is marked retraction of the chest with dullness, diminished fremitus and decreased breath sounds. In the later stages the process perforates the chest wall, forming first a subcutaneous abscess, or invades some contiguous organ. The patient's general condition gradually fails, the fever becomes higher and chills and sweats are common. Amyloid disease may cause enlargement of the liver and spleen and a richly albuminous urine. The disease is usually fatal in from twelve to eighteen months. Sometimes the course is much more acute, at other times protracted to three or four years.

The sputum is often bloody, even in the early stages of the disease. Hemorrhage is not uncommon and occasionally is profuse. Perforation of the chest wall almost regularly occurs. The subcutaneous abscesses that form before perforation occurs give a characteristic sensation; they are hard, semi-elastic tumors of uneven consistency which do not fluctuate. They are very sluggish and may be present a long time before they rupture.

The diagnosis of pulmonary actinomycosis can be made in the early stages only by discovering the organism in the sputum. In later stages it is distinguished from tuberculosis, carcinoma, bronchiectasis, abscess, etc., with difficulty. Extreme retraction of the chest should suggest actinomycosis. When subcutaneous tumors form and after rupture has occurred, the diagnosis is usually easy.

The X-ray shows no characteristic picture. Its greatest service is to demonstrate that early symptoms are due to a localized pulmonary disease and not to a simple bronchitis. The nature of the process it does not reveal. There is usually great increase in the hilus shadows and circumscribed areas suggesting tumor or diffuse infiltration resembling tuberculous lesions.

Treatment.—The disease is almost uniformly fatal. One instance of apparent recovery is reported. Iodid of potassium in large doses is said to cure over half of the cases in cattle and many bone and abdominal cases in man. While no undoubted instance of the cure of pulmonary actinomycosis by potassium iodid is reported, the symptoms are often greatly improved. A number of cases have been cured by operation, sometimes by simple drainage of a pleural exudate, sometimes by drainage and extirpation of the wall of the cavity with the cautery. Surgery offers the only prospect of complete recovery. With earlier diagnosis and improved operative technic the number of cures will increase.

Streptothricosis

This rare pulmonary infection is caused by an organism widely distributed in nature outside of the body and variously named cladothrix, oöspora, pseudotubercle bacillus, atypical actinomyces and nocardia. The term streptothrix is usually employed in spite of technical objections. It is probable that a number of varieties exist, but they are not yet clearly differentiated. The organism grows as long slender filaments, often in loose meshes, and the filaments show true branching. It stains with the ordinary aniline dyes, is Gram positive and resists decolorization by acids and to a less degree by alcohol. Its acid-fastness is less marked than that of the tubercle bacillus. It grows well aerobically on nearly all of the usual culture media at body and at lower temperatures. (See Vol. V, Chap. XXIV.)

In the lungs the organism causes bronchopneumonic and indurative lesions leading often to bronchiectasis, abscess and gangrene. There is nothing distinctive about the lesions and the diagnosis cannot be made without finding the organism. Sometimes nodules similar to tuberculous nodules are formed and the pulmonary lesions may closely simulate tuberculosis. Clinically the disease manifests itself as an acute or subacute bronchopneumonia, a chronic indurative pulmonary disease or a chronic pleurisy. In the acute bronchopneumonic form there is fever, cough and sputum which is often hemorrhagic. Usually the pulmonary condition is a part of a general sepsis and numerous abscesses form in the skin and other organs. The organism may be cultivated from the blood. In the chronic form the clinical picture is the same as that of chronic pulmonary tuberculosis. The disease is usually situated in the lower lobes and this localization is the only clinical symptom that may serve to distinguish it from tuberculosis. The pleural symptoms are secondary to the pulmonary involvement. An empyema forms which is drained but refuses to heal, leaving a chronic suppurating pleural cavity which may also communicate with the lung.

There is no sure way to diagnose the disease, except by discovery of the organism. The clinical symptoms are those of pulmonary tuberculosis except for the usual localization in the lower lobes.

Treatment for the condition is the same as the treatment for tuberculosis. Empyema, abscess and gangrene must be treated surgically. Recovery has been reported even in instances in which the organism has been cultivated from the blood.

Aspergillosis

A number of different moulds occasionally attack the lungs. The most frequent variety is the aspergillus fumigatus; far less commonly the mucor corymbifer. The former variety alone deserves special consideration. Usually it occurs as a secondary invader in pulmonary tuberculosis or other destructive pulmonary disease, but it may affect the lungs primarily, causing ulcerative and suppurating lesions. (See Vol. V, Chap. XXIV.)

The fungus grows readily on culture media in the form of a mould producing colonies of varying color. The hyphae segment and send off long filaments which are covered at their extremity with spores. The fungus is widely distributed in the outer world and may be found on vegetables, grains, bread, etc. It not infrequently attacks the lungs of birds producing extensive disease. Animals are also infrequently affected. Men are supposed to become infected by inhaling the spores. Dieulafoy, Chantemmesse and Widal report the disease in three pigeon feeders. These men hold the food in their mouth and blow it into the mouth of the pigeon. Renon reports the disease among hair sorters, ascribing the infection to the rye flour used in preparing the hair.

When the aspergillus is located in the lung it produces an area of necrosis surrounded by a zone of infiltrating leukocytes and pneumonic exudate. Fibrosis occurs but never to the same extent as in actinomycosis. The greatest growth of the mould occurs about the bronchus, probably on account of the free access of oxygen. Spore formation is particularly marked in this neighborhood, and the spores further infect neighboring parts of the lung. The necrotic portion of the lung is sequestered from the uninfected portion and is expectorated leaving a ragged cavity, which differs from a gangrenous cavity in the absence of putrid odor. It is possible that aspergillus prevents the growth of putrefactive bacteria. Occasionally aspergillus grows upon the mucous membrane of the trachea and bronchi without producing pulmonary lesions.

The symptoms of aspergillus infection present nothing characteristic, the diagnosis can be made only by finding the organism in the sputum. In tuberculosis and other chronic pulmonary diseases the secondary invasion of aspergillus adds nothing important to the clinical symptoms. When the disease affects the lungs primarily the symptoms are those of chronic ulcerative tuberculosis. A bronchial form is described which runs the clinical course of a chronic bronchitis.

The disease when once well established usually terminates fatally. The infection may subside at any stage of its course, leaving the patient with persisting symptoms due to the lung damage.

Treatment consists in the use of the general measures appropriate for the treatment of tuberculosis. Inhalations of creosote, of turpentine and of other aromatic substances are advised. Potassium iodid and arsenic are also recommended.

Blastomycosis

Infection of the lungs is only a part of a systemic infection. In some cases the disease has started from a pulmonary infection. The organism belongs to the species oidium and is also called monilia, eudomyces and saccharomyces. In tissues it appears as an oval or spherical body, seven to twenty microns in diameter, enclosed in a double contour hyalin capsule. The organism is Gram positive and grows well on artificial media. In cultures the growth of mycelia and spore bearing hyphae is observed. (See Vol. V, Chap. XXIV.)

The organism causes granulomatous and suppurative lesions that affect the skin and the internal organs. The pulmonary lesions somewhat resemble tuberculosis. They show small miliary or pea-sized abscesses which coalesce to form larger areas of softening. The arrangement is that of bronchopneumonic lesions. Large cavities may form. The bronchial lymph glands, the trachea, the larynx, the pleura may be involved.

The pulmonary involvement is a part of the systemic infection which runs the course of a pyemia. The pulmonary symptoms and signs are proportionate to the extent of pulmonary involvement. Skin lesions and lesions in other organs are always associated with the pulmonary lesions.

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CHAPTER IV

MASSIVE COLLAPSE OF THE LUNG

By SIR JOHN ROSE BRADFORD

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Massive collapse of the lung is an unusual condition in which the lung, without the presence of any gross lesion such as bronchial obstruction, pleural effusion, etc., interfering with the free entry of air, becomes airless to a greater or less degree and therefore useless for respiratory purposes.

This collapse involves varying amounts of the lung in different cases, usually an entire lobe or a very large portion of one lobe, and not infrequently the whole of one lung. Symptoms may be present or absent; in the former case they are sometimes of extreme urgency, but more frequently they are only of moderate severity. When symptoms are absent, as is by no means rare, the lesion may be entirely overlooked unless the chest is carefully examined.

Massive collapse is only seen as a complication of other diseases and of injuries, and this is a further reason why its real nature is often overlooked and the signs found in the chest attributed to other causes.

Etiology

In civil practice, massive collapse is most often seen as a sequel to certain abdominal operations, and more especially, operations for appendicitis and for hernia, but it may occur after any operation involving laparotomy. Such cases are, however, of complex character, inasmuch as in many a more or less prolonged anesthesia had been induced, and in some it is difficult to gauge the extent of the inflammatory lesion involving the peritoneum. Thus the diaphragm may be affected either directly or indirectly by any peritonitis present and so lead to inadequate respiration. Impairment of the respiratory movements of the diaphragm may be a cause of massive collapse, as is shown by the fact that massive collapse may result from the paralysis of the diaphragm seen in diphtheritic neuritis. Prolonged anesthesia may induce the retention of secretions in the bronchial tubes and thus lead mechanically to the production of massive collapse, and paralysis of the diaphragm might operate in an analagous manner. Hence in considering the etiology of massive collapse, the study of other varieties of the affection may be of more service. Some of the most striking forms are seen as the immediate or direct result of injuries, both in civil and in military practice. Thus it may follow such injuries as fracture of the pelvis or of the femur, but here also the problem is complex, since the severity of the injury may cause the patient to be so immobilized that the respiratory movements may be greatly hampered by the restraints imposed by posture. The conditions are much more simple in the large series of cases where the massive collapse has followed gunshot wounds, and it is this type of case that affords not only the simplest but also the most complete and extensive examples of massive collapse of the lung. Massive collapse may occur as a result of a gunshot wound where no anesthetic has been given in the course of the treatment of the wound and where the wound has been so slight that the patient has not been confined to bed prior to the onset of the collapse. Further, the soldier has been in perfect health, with no suggestion of previous lung disease, up to the time of wounding; thus such cases are peculiarly suitable for the study of the condition.

Gunshot wounds of the chest are especially liable to cause massive collapse of the lung, and it is probable that it occurs in at least five to ten per cent. of such injuries; it is possible that the incidence is really much higher, as the condition is often overlooked unless specially searched for. Collapse may occur in cases of unilateral gunshot wounds of the chest, either on the wounded side or on the opposite and non-wounded side, *i.e.*, contralateral massive collapse, or on both sides. The wound causing it may be severe or trivial, penetrating or non-penetrating. It is especially important to note that massive collapse, involving the whole of one lung, may occur as the result of a non-penetrating wound of the chest wall, without the presence of any extensive smashing of the chest wall or even without any fracture of ribs. Further, it may be of the contralateral type, and not only is this the case, but there may be no injury to the thoracic contents on the side wounded, the local injury being confined absolutely to the chest wall.

The wounds are not confined to those involving the lower chest walls; thus extreme massive collapse has been seen after a contour wound with the entry wound over the manubrium and the exit over the acromial end of the clavicle, but without any fracture of bones.

Non-penetrating wounds, limited to the abdominal wall, may also produce massive collapse of the lung, and it is occasionally seen as a complication of wounds of the buttocks, pelvis and thighs. No case of massive collapse as a sequel of a gunshot wound of the head or of the arm has fallen under the observation of the writer. In the case of wounds of the buttocks and of the thighs the causation may be complex, in that the injuries are often severe and frequently of such a nature as to necessitate a constrained posture of the patient, often for considerable periods, and so lead to restraint of the free movements of the chest. Massive collapse may be fully established within twenty-four hours of the infliction of the wound, but the opportunities for determining the earliest period of its onset have been scanty. Complete massive collapse involving one entire lung and of the contralateral type, the result of a non-penetrating wound of the chest wall of very slight severity, has been observed fully established, within fourteen to sixteen hours from the time of wounding. In this instance the soldier walked four miles after being wounded. It is thus clear that the essential factor in the etiology is the wound, and that the condition may ensue, even in its most marked form, where other supposed factors, such as anesthesia, posture, injury to the diaphragm or its nerves, exudation, secretion, or blood in the bronchial tubes can be excluded.

In rare instances, massive collapse may occur in association with pneumonia; thus a lobar pneumonia involving the upper lobe may be accompanied by complete collapse of the lower lobe, without the presence of any gross lesion, such as pleural effusion, etc. Massive collapse of the contralateral type is a not uncommon complication of unilateral hemothorax, but it would seem to be either unknown or very rare as a complication of pleural effusion, and no such case has fallen under the observation of the writer.

Varieties of Massive Collapse of the Lung

In cases of traumatic origin, such as those following unilateral gunshot wounds of the chest, the massive collapse may be homolateral, bilateral or contralateral, and this applies equally whether the wound be penetrating or non-penetrating. The homolateral variety is often the most difficult to recognize, as there must often be some doubt as to the presence or not of some gross lesion, such as a small hemothorax, since such a condition may be present, even when the wound is a non-penetrating one. The contralateral variety following a unilateral non-penetrating wound of the chest wall is on the whole the most striking clinical form. Massive collapse may be partial, lobar, or total in its distribution. In the partial type the upper and middle thirds of one or of both lower lobes are the parts most frequently involved. In the lobar type, one or both lower lobes are affected, and this is the most common form, but the upper lobe may be the only part of the lung involved. In the variety described as total the whole of one lung is affected. Massive collapse not only varies in the extent of the area of the lung involved, but also in the degree of airlessness produced; in all cases the physical signs suggest that no air enters the alveoli, but in some cases the finer bronchial tubes would seem to be pervious, while in others there is complete silence during inspiration over the area of lung involved. When the area of lung involved is small, there may be some increase in the size of the area while the patient is under observation, but more usually the condition is fully established at the time when it is first detected. Another and much more frequent variation is a change in the degree of airlessness of the lung; this diminishes and the weak or absent breath sounds are replaced by loud tubular or amphoric breathing; less frequently the change is in the reverse direction.

Massive collapse of the lung may be the only lesion present in gunshot wounds of the chest, but in a much larger number of cases, it is associated with some other lesion and more especially with hemothorax. In cases of unilateral hemothorax the collapse may be either homolateral or contralateral, and the commonest form of the latter variety is that associated with hemothorax. This association is far more frequent than the occurrence of contralateral collapse as a result of a non-penetrating unilateral wound limited to the chest wall.

Homolateral massive collapse associated with hemothorax is often difficult to recognize, since it is obvious that the bloody effusion in the pleural cavity may itself be answerable, at any rate, for some of the pulmonary collapse present. There is, however, one type of these cases that is easily to be recognized, that in which a very small hemothorax of only a few ounces is associated with massive collapse involving the whole of the lung on the wounded and affected side. Such cases, where the collapse present is absolutely out of proportion to the pleural lesion and where pneumothorax is absent, merge into others where the collapse exists without any collection of fluid in the pleural cavity.

Physical Signs of Massive Collapse of the Lung

The signs are most marked and most easily recognized in cases of contralateral collapse involving the whole of one lung, the result of a non-penetrating wound of the chest wall limited to one side of the chest, and causing no lesion to the thoracic contents on the injured side. In such a case the wound is not only absolutely limited to one side, but there is also no question of a foreign body having penetrated and lodged on the side opposite to that wounded, since the foreign body may have been found in the wound, removed and direct evidence obtained that the wound is strictly limited to the chest wall. In other cases the wound has been of so trivial a character that the foreign body has dropped out on removing the patient's clothes and the wound itself has healed rapidly. Physical examination reveals no lesion of the lung or exudate in the pleural cavity on the wounded side, and this may be confirmed by X-ray examination. Striking signs, however, are present on the opposite side. The cardiac impulse is greatly displaced towards the affected side and away, therefore, from the wounded side, the displacement is lateral and upward, the lateral displacement being usually far the greater. If the left be the affected side, the apex beat may be found in the axilla, if the right the impulse may be felt in the right nipple line. There is often marked displacement of the impulse upward, and it may be palpable as high as the third rib. The area of visibility of the cardiac impulse may also be increased greatly in extent. The affected side of the chest is retracted and immobile, and the ribs can be seen and also felt to be closer together than on the normal side. The dome of the diaphragm on the affected side is also much higher than normal and the displaced diaphragm is immobile on the affected side. The high level of the diaphragm can be readily demonstrated on the left side by percussion; this method is not so satisfactory on the right side, but X-ray observation not only demonstrates the high level of the diaphragm but also reveals its immobility on the affected side. The percussion note is impaired all over the affected side, and dullness, marked in amount, may be present up to the level of the clavicle. In the left axilla resonance to an abnormally high level is present owing to the altered position of the diaphragm. Tactile vocal fremitus is either diminished, absent or increased. If diminished or absent, the breath sounds are also diminished or absent; if increased the breath sounds are tubular or amphoric in character. In such cases bronchophony and pectoriloquy are exceedingly well marked, and whispering pectoriloquy may be heard with great distinctness over a wide area. Thus two groups of cases may be recognized, one with diminished or absent tacticle fremitus and breath sounds, and one with increased tactile fremitus, together with tubular or amphoric breathing and with bronchophony and pectoriloquy. In both cases extreme displacement of the heart is present. The great bulk of cases conform to the type with increased tactile fremitus and tubular breathing, but some cases, and more especially those seen early, have weak or absent tactile fremitus and breath sounds. The signs, however, are apt to change in one and the same case; thus at first weak or absent breath sounds may be present, and twenty-four hours later these are replaced by loud tubular or amphoric breathing, with increased tactile fremitus. Such changes may occur without any alteration in the degree of displacement of the heart. The alteration in the physical signs is commonly of the nature just described, but sometimes a change takes place so that tubular breathing, etc., is replaced by weak or absent breath sounds, and such alterations may occur more than once in the clinical course of the case. These repeated alterations are evidently dependent upon variations in the patency of the bronchial tubes, and are seen in the later stages of the condition when the chest wall is no longer immobile and some degree of re-expansion of the lung is taking place. They present resemblances to the well-known variations in the physical signs that occur in cases of bronchiectasis.

Râles and adventitious sounds may be present, but they are often absent throughout the clinical course of the most marked cases, even those involving the whole of one lung. Adventitious sounds may, however, be a prominent sign in the later stages of some cases when the lung is re-expanding. They are also present when inflammatory complications, such as bronchitis, pneumonia or pleurisy, develop in the collapsed lung. These signs are not essential signs of massive collapse as such; they are more usually to be associated either with re-expansion of the lung or with the development of inflammatory complications. Displacement of the cardiac impulse is certainly the most important as well as the most characteristic sign of massive collapse; the condition cannot be diagnosed with certainty unless this displacement is present. It is usually very considerable in amount and is always towards the collapsed lung. Its duration varies; sometimes it is more or less transitory and considerable changes in the position of the apex beat may occur within periods as short as twenty-four or forty-eight hours. On the other hand, it may be very persistent, and three or four weeks may elapse before the heart returns to its normal position. Extreme cardiac displacement may be present without the patient being aware of it, or even having any cardiac symptoms. When massive collapse involves either the entire lung or the upper lobe alone, the cardiac displacement is upwards as well as lateral. In cases of extreme cardiac displacement, examination of the lung usually reveals the presence of tubular or amphoric breathing, but sometimes with displacement of the heart equal to that seen in transposition of the viscera, the lung signs are of the type with weak or absent breath sounds. Such cases may be difficult to recognize, if sufficient importance is not attached to the mere weakness of the breath sounds. The heart returns towards its normal position before the signs in the lung have disappeared, and it is not uncommon for the impulse to be in the normal position at a time when there is still an area of dullness with tubular breathing and pectoriloquy at the affected base. Thus it is evident, that an area of collapse too small to cause obvious cardiac displacement, may yet give rise to well marked pulmonary signs.

In cases of massive collapse of less extent and involving only one lobe or a portion of one lobe, the signs are similar to those just described, but they are necessarily more limited in area, and the cardiac displacement, although present, is not so great as that seen in cases of collapse involving the whole of one lung. The high level and immobility of the dome of the diaphragm are, however, always striking features of these cases.

The physical signs may be summarized by saying that the pulmonary signs present a considerable resemblance to the well-known signs of consolidation; if anything they are rather more marked, especially in the tubular or amphoric character of the breath sounds; these signs are, however, accompanied with retraction and immobility of the chest wall together with displacement of the heart and of the dome of the diaphragm. These characteristic signs sharply differentiate cases of massive collapse from other pulmonary lesions and from pleural lesions.

In the other forms of massive collapse, the signs are essentially similar to those described above as occurring in the cases resulting from gunshot wounds of the chest, but it may be that the form most usually seen in civil practice after abdominal operations, is of a somewhat different type, in that inflammatory complications, such as pleurisy, pneumonia, etc., affecting the collapsed lung, occur more often, and hence râles and adventitious sounds are more frequently heard. Similar inflammatory complications, however, do occur in the cases following gunshot wounds.

Symptoms of Massive Collapse of the Lung

These vary greatly in severity in different cases, and on the whole tend to be most marked at the onset of the condition, subsiding early and even disappearing provided the patient is kept at rest in bed. It is important to recognize that massive collapse may involve the whole of one lung without the presence of any urgent symptoms, and the condition may be overlooked unless the chest is carefully examined, and this is more especially the case in the contralateral variety of the affection. If such cases are not recognized and the injured side of the chest be operated on and the pleura opened freely, sudden death may occur. Dyspnea is the most constant symptom in massive collapse; it is usually of moderate severity but is greatly increased on exertion and even by such slight exertion as sitting up in bed. In rare instances an urgent dyspnea, comparable to that seen in pulmonary embolism, has been described. Cough, usually slight, but often repeated and persistent, may be present together with expectoration of a muco-purulent character. The cough and expectoration are more marked in the postoperative civil cases than after gunshot wounds. In the latter cases all expectoration may be absent throughout the duration of the condition, and no history of an expectoration or of hemoptysis after being wounded can be obtained. This is a point of some importance with regard to the causation of massive collapse. The absence of symptoms is most marked in cases of collapse involving the entire lung; in cases where a lobe or a portion of a lobe only is affected, cough and expectoration are more frequently present. Pyrexia is often absent, and when present may be due to some other lesion, but pyrexia is necessarily present in the cases where pneumonia, pleurisy, etc., develop as complications of massive collapse.

Duration of Massive Collapse of the Lung

The duration of massive collapse is very variable. In some cases the signs clear up in a few days and the heart may return to its normal position in from one to three days after a displacement of the impulse of as much as two inches, but even in these cases pulmonary signs, such as a localized area of tubular breathing, together with retraction of the chest wall and some limitation of respiratory movement, may persist for some days. The more usual course of these cases is more gradual, and some three weeks may generally elapse before the return to the normal is complete. The immobility of the chest disappears and the breath sounds become less tubular and are accompanied with abundant adventitious sounds, such as crepitations and râles. Cough and expectoration, usually watery and mucoid, sometimes purulent, but never rusty, are also present, and sometimes the expectoration is not only watery but so abundant as to suggest, together with the signs, the presence of edema of the lung, but this has not, as yet, been confirmed by post-mortem examination; the lungs examined have only shown evidence of extreme congestion.

Complications in Massive Collapse of the Lung

Bronchitis, especially the purulent variety, pleurisy and pneumonia are the most common complications of massive collapse, and definite clinical and post-mortem evidence of their occurrence has been obtained. It is probable that, in some cases, edema of the lung may occur during the stage of re-expansion, but absolute proof of this has not as yet been obtained.

Purulent bronchitis, limited absolutely to the collapsed lung, has been found post-mortem, and this is rather remarkable, seeing that in the collapse dependent upon hemothorax inflammatory complications and bronchitis are rare. Although purulent bronchitis is a frequent complication of hemothorax, the lung collapsed beneath the effusion is far less affected than the rest of the lung. In massive collapse the opposite may obtain and the bronchitis be limited to the collapsed lung. Pleurisy is not an uncommon late complication of massive collapse; it is usually dry, but effusion may occur. Such cases could scarcely be recognized unless seen in an early stage when collapse only is present, although when the effusion has supervened, the heart may still be displaced towards the side of the effusion owing to the extent of the collapse and the small amount of the effusion.

Pneumonia of the lobar type occasionally occurs limited to the collapsed lobe; in such cases the development of the pneumonic consolidation is accompanied by a return of the heart's impulse towards its normal position.

Diagnosis of Massive Collapse of the Lung

Contralateral massive collapse, the result of unilateral non-penetrating parietal wounds, is generally not difficult to recognize. Such cases may be confused with congenital displacement of the heart, or with the results of some former and forgotten chest illness. The characteristic physical signs and the return to the normal after the lapse of a few days or, at the most, of two or three weeks, afford convincing proof of the true nature of such cases. When contralateral collapse occurs in association with hemothorax on the wounded side, the difficulties of diagnosis are much greater. Two errors are especially likely to be made. The cardiac displacement is apt to be attributed entirely to the presence of the hemothorax, when, in reality, it is mainly dependent upon the contralateral collapse; and, secondly, the lung signs, tubular breathing, etc., are attributed in error to the supposed presence of pneumonia. The high level of the diaphragm, together with its immobility on the affected side, affords the key to the interpretation of these cases. The following are some of the more common errors of diagnosis in cases of massive collapse involving either the whole of one lung or the entire lower lobe. The high level of the diaphragm and the upward displacement of the heart may be attributed to the supposed existence of a subphrenic collection of gas and fluid, when in reality none is present. The absence of abdominal symptoms and the presence of chest signs are usually sufficient for this error to be avoided. The great displacement of the heart may be attributed to a pleural lesion on the wounded side when none is present, the wound being really limited to the parietes. The cardiac displacement may be attributed to cardiac dilatation and the pulmonary signs entirely overlooked, or the displacement of the heart may be thought to be of congenital origin owing to the absence of symptoms. The increased resonance at the left base, due to the upward displacement of the diaphragm, may be attributed to the supposed presence of pneumothorax or to a subphrenic collection of gas. Such mistakes may be avoided by paying attention to the direction of the cardiac displacement and also to the fact that the affected side is retracted and not bulged.

Massive collapse, occurring by itself or on the same side of the chest as the injury, is most apt to be confounded with pneumonia, and this error is frequently made and can only be avoided by a thorough study of the physical signs, and by specially noting the cardiac displacement. For purposes of diagnosis, three stages with different physical signs may be recognized. In the first, the signs consist of marked retraction and immobility of the affected side with great displacement of the cardiac impulse and of the dome of the diaphragm, together with absent or weak breath sounds over the area of lung affected. In the second stage, the signs are similar with the exception that the weak breath sounds are now replaced by loud tubular or amphoric breathing with bronchophony and marked pectoriloquy. The cardiac displacement may be slightly less, and sometimes there is no longer complete immobility. In the third stage, or stage of re-expansion, the characteristic feature is the development of numerous adventitious sounds over the area of lung involved, and now the heart is less displaced and the movement of the affected chest is more obvious.

X-ray examination is of the greatest possible value in the investigation of these cases and should always be employed if possible.

Morbid Anatomy of Massive Collapse of the Lung

The observations on the morbid appearance of these cases are scanty. The lung or portion of lung affected is obviously shrunken, heavy, leaden blue in color and airless. Frequently it is greatly congested. No obvious gross obstruction of the bronchi is present, and complete massive collapse involving the whole of one lung may be present without any evidence of the existence of any gross obstruction of the main bronchus, such as the presence of a blood clot or foreign body. Obstruction of the bronchus by a blood clot or foreign body is of course capable of producing a condition very similar to that of extensive massive collapse, but there is definite post-mortem evidence that such is not the explanation of all cases of massive collapse.

Causation of Massive Collapse of the Lung

The mode of production of massive collapse is obscure. Theoretically it might ensue either as a result of bronchial obstruction or else as a sequel to impairment of the efficiency of the respiratory movements. This in turn might result from definite respiratory paralysis, as in paralysis of the diaphragm in diphtheritic neuritis, or possibly from a temporary paralysis of the inspiratory mechanism of reflex origin. There are difficulties in accepting either of these views. Thus there is often no clinical or post-mortem evidence of bronchial obstruction, and it is particularly difficult to explain the frequent absence of symptoms if the obstruction is of bronchial origin. On the other hand, it is not easy to understand why a comparatively trivial injury of one side of the chest should produce a reflex palsy of the respiratory muscles on the opposite side of the chest, but on the whole it would seem that this explanation is the more probable.

Treatment of Massive Collapse of the Lung

The condition calls for no special treatment beyond encouraging, so far as the condition of the patient allows, the free movement of the chest in respiration. Massive collapse derives its main importance from the liability to confuse it with pneumonia, cardiac disease, etc., and in some cases with other pulmonary or pleural lesions, *e.g.*, abscess of the lung. The erroneous diagnosis may lead to the adoption of methods of treatment not only unnecessary but sometimes dangerous, *e.g.*, exploratory thoractomy.

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CHAPTER V

DISEASES OF THE PLEURA

By JOSEPH A. CAPPS

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Diseases of the pleural membranes may be classified under the following heads:

I. Pleurisy—inflammation of the pleura.
II. Non-inflammatory fluids in the pleural cavity—Hydrothorax, Hemothorax and Chylothorax.
III. Pneumothorax—air or gas in the pleural cavity.
IV. Neoplasms of the pleura.
V. Echinococcus of the pleura.

I. PLEURISY

Pleurisy or pleuritis is an inflammation of the pleural membranes that may involve their visceral, parietal or diaphragmatic coverings.

Etiology

The inflammatory signs may be confined to the pleura, in which case it is spoken of as *primary*. The simplest form follows exposure to cold. In all probability the majority of these pleurisies are not truly primary, but represent the localized flaring up of an old inflammatory process in the neighboring tissue of lung or glands. Photographs with the X-ray reveal the presence of old tuberculous areas in the region of many pleurisies, wherein the ordinary methods of diagnosis present only the evidence of the pleural involvement. The tuberculous pleurisy is perhaps always secondary to an older focus of infection.

Secondary pleurisy has its origin in (1) extension of inflammation from the lungs, especially in pneumonia, tuberculosis, pulmonary abscess, and infarcts; (2) extension of inflammation from adjacent organs and structures, notably in pericarditis, mediastinitis, bronchial lymphadenitis, and following perforation of the diaphragm from liver abscess, or cancer of the stomach; (3) metastatic infection from tonsillitis, articular rheumatism or general septicemia; (4) association with chronic diseases such as nephritis, leukemia and gout.

The lung, enveloped as it is by the visceral pleura, is responsible for the greatest number of pleurisies. Nearly every form of inflammation of the lung involves the pleura sooner or later, whether it be pneumonia, tuberculosis, abscess or infarct. Frequently the pleuritis is obscured by the overshadowing signs of pulmonary inflammation, though the presence of pain is always indicative of pleural involvement.

Bacteriology.—The exact determination of the bacteria responsible for pleurisy is not always possible. The sputum and the pleural exudate offer the best material for examination. But in both media, secondary invaders may dominate over the original organisms. The bacteria commonly found are the tubercle bacillus, pneumococcus and streptococcus.

The frequency of old adhesions found at necropsy in the vicinity of tuberculous lesion of the lung attests the important role of the tubercle bacillus. Tubercle bacilli have been demonstrated in from 22 to 85 per cent. of serous effusions, according to Lord[1], either directly or by inoculation experiments.

Fibrinous exudates occurring with acute pulmonary infections are more often due to pneumococcus or streptococcus. Most of the empyemas complicating the pneumonias during the recent influenza epidemic yielded cultures of streptococcus; a smaller proportion showed pneumococcus, and a few, staphylococcus.

Other organisms occasionally recovered from pleural exudates are Friedlander's bacillus, influenza bacillus, diphtheria bacillus and typhoid bacillus. It is interesting to note that pleurisy is relatively rare in three diseases in which pulmonary complications are often present, influenza, measles and typhoid fever. The leukopenia characteristic of these infections may offer an explanation of this fact. Mixed infections of pyogenic organisms with tubercle bacilli are common, and often when cocci only can be found in the exudate a primary tuberculous inflammation may be diagnosed by the general physical findings.

Morbid Anatomy

The inflamed pleura is at first congested and acquires a dull, lusterless appearance. Soon an exudate of fibrin of varying thickness forms, and this gives rise to the friction sounds heard over the chest during the respiratory movements. At this stage absorption and organization may take place, leaving adhesions or scar tissue that are permanent. In the majority of instances the fibrinous exudate is followed by a serous effusion, at first clear, and later often cloudy from the presence of leucocytes and red cells. The usual course of serous effusion is a slow absorption and recovery, but if the outpouring of pus cells is excessive and continuous, the fluid becomes purulent and empyema develops. Nature's attempts at absorbing pus are usually unsuccessful without surgical intervention.

Clinical Pathology

The study of pleural effusions gives important information concerning the origin and nature of the affection. In the first place it is essential to differentiate between a transudate and an exudate.

A *transudate* is caused by a circulatory disturbance, stasis in the pulmonary vessels, and is non-inflammatory in character. The fluid is usually clear, of low specific gravity (1.010 to 1.015), and has a low protein content (less than 30 grams per liter). The number of cells present under the microscope is small, and they are chiefly endothelial cells and lymphocytes. The fluid is generally free from organisms.

An *exudate* is of inflammatory origin, and as it is rich in protein (over 40 grams per liter) the specific gravity is high (over 1.015). Bacteria are usually present in smears or cultures, though not always numerous. The abundance of cellular elements not only shows that the effusion is inflammatory but indicates roughly the nature of the inflammation. In the acute infections excited by the pyogenic organisms, pneumococcus, streptococcus and staphylococcus, polynuclear leucocytes predominate. In tuberculous effusions lymphocytes are characteristic, although during the early stage of the infection many polynuclear cells may also be present. If red corpuscles are at all numerous in the fluid, the evidence in favor of a tuberculous infection is further strengthened.

The effusion association with tumors of the pleura also exhibits blood, often in large amount. Tumor cells are not often found or easily identified. Dock[2], however, considers the presence of many cells undergoing mitosis a significant finding. The "seal ring" cells with eccentric nuclei are also characteristic of neoplasms.

Eosinophils are occasionally encountered, but their significance is unknown. Clinical experience with cytological examinations not infrequently leaves us in doubt concerning the nature of the effusion. Mixed infections contribute to this uncertainty, especially when tuberculous infection is complicated by invasion with pyogenic organisms. Lymphocytes cannot be accepted as pathognomonic of tuberculosis, since they have been found by both Miller[3] and Lord[1] when the tuberculin reaction was negative. Cytodiagnosis must be looked upon as a valuable method, provided it is properly controlled by other clinical evidence.

The Absorptive Power of the Pleura.—Absorption of an exudate is a complicated process in which many biochemical and pathological factors participate. The integrity of the pleura, the nature of the effusion, the formation of enzymes, the state of the general circulation, all enter into the problem. The channels through which the products of absorption flow are the endothelial cells lining the pleura, the blood vessels and the lymphatics.

Fibrin is reduced to a state of liquefaction preliminary to absorption. Opie[4] has described an enzyme produced by polynuclear cells, called nucleoprotease, which digests fibrin in an alkaline medium and prepares it for absorption. Other formed elements go through a like process of digestion.

Fluids are taken up under certain conditions by the blood. Starling[5] has called attention to the fact that a hypertonic salt solution introduced into the pleural cavity is followed by an increase in the fluid content within a few hours. *Per contra* a hypotonic salt solution is rapidly absorbed. Thus the flow into or out of the pleural cavity seems dependent on osmotic pressure. "So long as any difference in composition exists between the intra and extra vascular fluids, so long will diffusive currents be set up, tending to equalize the difference." But an osmotic salt solution is also absorbed with a rapidity equal to that of the hypotonic solution, a fact explained by Starling by the rich content of protein in the blood plasma. "Thus we may conceive that there is normally a balance in the capillaries between the processes of exudation and of absorption, the former being conditioned by the capillary blood pressure, and the latter by the difference in protein content, and therefore of osmotic pressure between the blood plasma and tissue fluids." The lymphatic system plays an important role in absorption. After injection of methylene blue into the pleural cavity, the color makes its way along the lymphatics of the costal and mediastinal pleura (not the visceral and diaphragmatic pleura). The current of the lymph stream is extremely slow and dependent upon the respiratory movements of the chest. For this reason when an effusion is large enough to impede the respiratory excursion, absorption by the lymphatics is limited. Long before the dye has made its appearance in the thoracic duct, the color is present in the urine, which emphasizes the comparative rapidity of blood absorption.

Now the experiments above mentioned were performed upon animals with a healthy pleura. From a clinical standpoint the conditions of the experiment are best simulated in man by the transudate in which the pleura is relatively normal. In exudates, the inflammation of the pleura involves the endothelial cells, lymph spaces and capillaries in a process of coagulation necrosis that cripples cell function and blocks the natural channels of absorption. Hence it is that in a thickly encapsulated or encysted effusion, there may be little or no diffusion. Absorption waits on a cleaning out of the blocked spaces by the action of digestive enzymes.

Emerson[6] concludes from his investigations that the pressure of a moderate effusion favors absorption, while that of an excessive amount interferes with this function because of the embarrassment to the return of venous blood to the heart and consequent fall of the systemic pressure. Small purulent exudates may be absorbed, but an empyema tends to break down the walls of the cavity and seek an outlet.

Intrathoracic Pressure of Effusions.—Pleural effusions usually collect first at the bases of the thorax and posteriorly, exerting pressure on the most dependent portions of the lung and causing atelectasis.

The rapid introduction of fluid into the pleural cavity of an animal causes little discomfort at first, but when the amount increases to a certain point cyanosis and dyspnea rapidly develop, the venous pressure rises, the arterial pressure falls and death ensues. This circulatory failure has been variously explained as due to displacement of the heart, kinking of the vena cava, or with a greater degree of plausibility, to a stoppage of the flow of blood to the heart by the pressure exerted on the vena cava.

The intrapleural pressure of fluids was determined by Quincke and found to vary from 0 to 26 mm. of Hg. But Gerhardt has shown that even in fair sized effusions the pressure is negative above the fluid and rarely positive at the upper level of the fluid. At lower levels the pressure is hydrostatic and proportional to the height of the fluid column. Therefore, the lower part of the lung, the base of the mediastinum and the diaphragm receive the maximum force of the pressure. When a massive accumulation does give rise to a general positive pressure in the affected side of the chest, alarming symptoms of dyspnea and circulatory collapse are likely to occur. Mobility of the bony thorax and a capacity of the opposite lung for compensatory expansion are influences that counteract the rise in the intrapleural pressure. This explains the greater tolerance of the young to large effusions than the aged.

Circulatory Disturbances Observed During Withdrawal of Pleural Effusions.—The intimate relationship of the pleural structures to the general circulation is better understood by considering the changes in blood pressure induced (1) by withdrawal of fluid and (2) by irritation of the pleural membrane.

1. Withdrawal of fluid by a hollow trocar or needle causes a moderate fall in arterial pressure, averaging about 20 mm. Hg[7]. Rapid withdrawal of a large amount increases the reaction, but the effect is usually quite transitory and harmless.

2. Irritation of the inflamed pleura has no constant influence on the blood pressure, but often its effect is alarming or even dangerous.

Lewis and the author[8] found that irritation of the pleura of healthy dogs produced little effect on blood pressure. In dogs, with artificially induced pleurisy, irritation of the visceral pleura by means of a sharp needle or chemicals, in some instances caused no disturbance; in others it induced considerable or even fatal fall in blood pressure. A study of the latter group exhibited two types of depressor reaction:

1. Cardio-inhibitory with slowing of the pulse, violent excursions in the tracings and slow respirations. This is quickly remedied by section of the vagus or administration of atropin. Even without treatment recovery is the rule.

2. Vasomotor, with rapid thready pulse and a steady fall in pressure that may terminate fatally.

In man similar symptoms of circulatory depression or collapse occur during paracentesis and occasionally during the irrigation of the pleural cavity with antiseptic solutions (notably formalin, hydrogen peroxide and Dakin's solution). They may appear immediately after the puncture or toward the end of the operation when the needle comes in contact with the expanding lung.

Pain Sense of the Pleura.—Of all the phenomena associated with pleurisy none deserves more consideration than the symptom of pain. Mackenzie[9] states that "the due recognition of the factors concerned in the production of pain is of the first importance in the study of disease." This observation applies with particular force to pleurisy, for pain is the most constant symptom and a valuable aid in diagnosis.

1. *Physiology of Pleural Pain.*—The nerve supply of the pleura is as follows: the parietal pleura receives its innervation from the intercostal,

sympathetic and vagus nerves; the visceral pleura is supplied by the nerve fibers from the pulmonary plexuses, which originate in the vagus and sympathetic nerves. The pericardial pleura receives branches of the vagus and of the phrenic nerves. The diaphragmatic pleura is penetrated on the outer side by the lower six intercostals and centrally is furnished by the phrenic nerve fibers, some of which are sensory (Ramström[10]).

Physiologists have contributed very little to our specific knowledge of the sensibility of the pleural membranes, since the investigation cannot be carried on successfully in animals, and these parts are not easily accessible in man. Nevertheless, it is to the physiologic researches of Mackenzie, Ross and Head that we are indebted for establishing the general laws underlying the production and distribution of visceral pain. The nerves supplying the skin and skeletal muscles have become so educated that any injury to them is accurately located. Such is not the case with the nerves of the internal organs. A painful irritation of the viscera finds expression, not necessarily over the site of the organ, but in a painful area of skin often remote from it. Head[11] has shown that the painful stimulus in the organ travels in a centripetal direction to the posterior part of the cord and there sets up excitation of the nerves which in the same and adjoining segments supply the peripheral surfaces with sensation. The pain is referred to the skin because therein the pain sense reaches its highest development.

Referred pain from the viscera has these characteristics to differentiate it from pain of peripheral origin:

1. It is often remote from the site of irritation.
2. It follows lines on the skin of spinal segmentation rather than the course of peripheral nerves.
3. It is usually associated with cutaneous hyperesthesia and tenderness to pressure.
4. Often the pain fails to involve a whole segmental area of the skin, but finds expression in one or more points of maximal tenderness and spontaneous pain.

These generalizations of Head stand today unquestioned, but his interpretation of thoracic pain has led him into error. Rightly he states that the pain of parietal pleurisy is local, following the course of the intercostal nerves. But the assertions that referred pains in pleuropneumonia arise from the lungs only, and that serous membranes do not give rise to referred pain, are disproved by clinical experience.

Lenander[12] considers the parietal pleura and pericardium to be highly sensitive to pain as well as the mediastinal tissues. He calls attention to the fact that because of the overlapping of the intercostal nerve-endings within the thorax, every point in the pleura may have fibers from at least two nerves.

2. *Experimental Production and Localization of Pain by Irritating the Pleura During Paracentesis.*—A simple method has been used by the author[13,14] for testing the sensation of the pleura during paracentesis. Through the hollow trocar a long dull pointed wire is inserted and the location of pain noted when pressure is applied to the various areas in the cavity. The observations made in thirty-five cases favorable to exploration lead to the following conclusions:

1. The *visceral* pleura is not endowed with pain sense.

2. The *parietal* pleura is richly supplied with sensory fibers from the intercostal nerves. Irritation of the pleura induces sharp pain that is accurately located by the individual over the spot that is touched. Such irritation in our experience never gives rise to referred pain in the neck or in the abdomen. The power to locate sensory impressions seems more highly developed in the anterior and lateral aspects than in the posterior.

3. The *diaphragmatic* pleura derives its sensory supply from two sources, the phrenic nerve and the last six intercostal nerves. The central portion of the diaphragmatic pleura is innervated by the phrenic nerve. (Fig. 1.) Irritation of this portion sets up pain in the neck. A peripheral rim of the diaphragmatic pleura, which is two or three inches wide anteriorly and laterally, and a segment corresponding to the posterior third of the membrane, are innervated by the sensory fibers of the intercostal nerves. Irritation of these areas gives rise to pain in the lower thorax, in the lumbar region or in the abdomen.

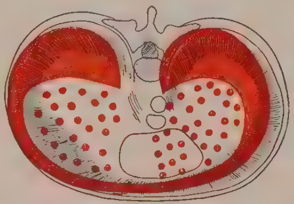

FIG. 1.—Composite diagram showing the sensory supply of diaphragmatic pleura (thirty-five cases). The margin in red supplied by intercostal nerves; the dotted area by the phrenic.

The neck pain arising from irritation of the central portion of the diaphragmatic pleura is a true referred pain, the afferent impulses reaching the cervical cord through the phrenic nerve trunk and exciting efferent impulses in the skin and superficial tissues supplied by the third and fourth spinal segments. This pain is characterized by a point of maximum pain and tenderness, and by a surrounding zone of cutaneous hyperesthesia and hyperalgesia. The maximum point of pain has a remarkable tendency to appear along the ridge of the trapezius muscle (fourth spinal segment). (Fig. 2.)

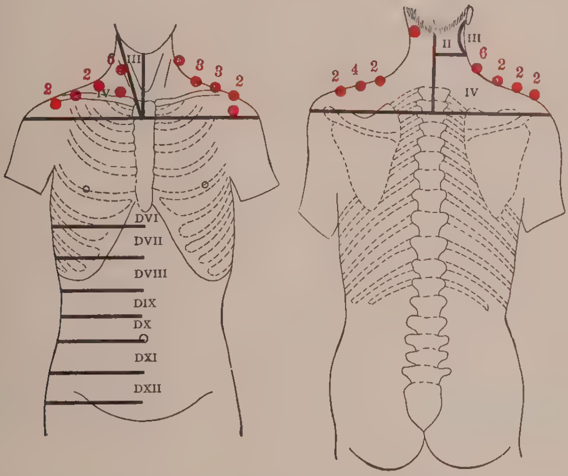

FIG. 2.—Location of maximum points of referred neck pain from diaphragm irritation in twenty-three cases. They all are situated in the regions supplied by the third and fourth spinal segments. Also areas of referred pain in abdominal wall.

The pain elicited by irritation of the peripheral or posterior portion of the diaphragmatic pleura is also a true referred pain. The pain is usually distributed in segmental areas over the lower thorax and epigastrium, sometimes extending downward over the whole abdomen on the same side (seventh to twelfth dorsal segments). (Fig. 2.) The pain is spontaneous and is associated with hyperesthesia and hyperalgesia of the skin and superficial tissues on pressure.

The distribution of the pain is determined by the degree of irritation and by the part that is touched. The more intense the irritation of the pleura, the greater the tendency of the pain to spread down over the lower abdomen. Rarely from strong pressure the pain is bilateral, extending over both sides of the abdomen. When the posterior portion of the diaphragmatic pleura is irritated the pain is most marked in the lumbar region.

4. The *pericardial pleura* receives its sensory innervation chiefly, if not exclusively, from the phrenic nerve. (Fig. 3.) Irritation of this part of the pleura is followed by pain in the neck of the same character and in the same locations as that induced by irritation of the central portion of the diaphragmatic pleura. This pain is a referred pain, characterized by

a maximum point of tenderness and pain, by hyperesthesia and hyperalgesia to pressure of the surrounding skin and by muscular rigidity.

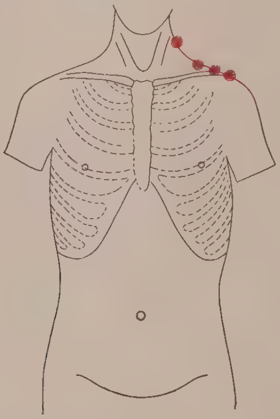

Fig. 3.—Location of points of maximum pain from irritation of pericardial pleura in five cases. All lie in fourth spinal segment.

Clinical Types of Pleurisy

The clinical course of pleurisy may end after the fibrinous stage or it may go on to the stage of effusion, or it may terminate in the formation of pus. For descriptive and diagnostic purposes three types are recognized:

1. Dry or fibrinous pleurisy.
2. Pleurisy with effusion.
3. Empyema.

In addition there are a number of atypical or special forms of pleurisy.

1. Dry or Fibrinous Pleurisy

Etiology

Dry or fibrinous pleurisy is an inflammation of the pleura associated with an exudate of fibrin. The causes of fibrinous pleurisy in the order of their frequency are the tubercle bacillus, pneumococcus and streptococcus. Most of the dry pleurisies are of tuberculous origin. A thick fibrinous exudate almost constantly accompanies acute lobar pneumonia. The fibrinous layer found with streptococcus bronchopneumonia and abscess may be either thin or massive.

Symptoms of Dry or Fibrinous Pleurisy

The onset may be announced by a chill and fever, particularly when the pleurisy is associated with pneumonia. In the tuberculous cases a chill is less common and the fever not so pronounced. Many tuberculous pleurisies give a vague history of loss of weight, slight fever, malaise and indigestion, symptoms that should lead to a careful examination of the chest. Pain is usually the first and chief complaint of the patient. It has a predilection for the axillary and lower anterior regions. Its severity varies from a dull ache to a sharp, stabbing sensation, depending on the degree of movement of the pleural surfaces. Because of the relative immobility of the lobe, an apical pleurisy rarely gives rise to severe pain, but more often to a soreness like rheumatism. On the other hand the pain of pleurisy of the middle and lower lobes, which make a wide excursion with respiration, is often excruciating in character. For the same reason diaphragmatic pleurisy is exceedingly painful.

The pain is aggravated by cough or deep inspiration. Often short unproductive cough is present, provoked by the irritation of the vagus nerve endings in the pleura. The pulse is accelerated and in severe cases other symptoms of general infection may appear, such as headache, muscular soreness, anorexia and fever.

Under favorable conditions the temperature and subjective symptoms subside in a few days, although for an indefinite period thereafter a "stitch" in the side may be induced by cough or violent movement of the chest.

Physical Signs of Dry or Fibrinous Pleurisy

The patient usually lies on the affected side or in a position that retards the respiratory movements on that side and breathes as far as possible with the opposite lung. The respirations are shallow and rapid, a protective mechanism. Sudden movements of the body are painful. The expansion of the diseased side is much restricted. Litten's diaphragm shadow, which is best observed by placing the foot of the bed toward the window and standing at an angle of 45 degrees from the feet, makes a limited excursion during inspiration, or is absent altogether. Dyspnea is evident when pain is excessive, but there is no cyanosis unless the pleurisy is a part of a pneumonic process.

Exceptionally a pleuritic rub may be felt. The "new leather" friction gives a sensation of grating to the palpating hand. Tenderness to pressure in the inflamed area is common. Percussion yields little information of value in dry pleurisy.

A friction rub heard during inspiration and at times during expiration affords conclusive evidence. The sounds are loudest over the lower part of the chest, where movement is greatest, and are least audible or absent over the apex, where mobility is slight. In the ordinary parietal pleurisy the friction is generally heard over the region in which pain is complained of by the patient. As already pointed out sensation in the parietal pleura is quite sharply localized to the part irritated, especially in the lateral and anterior areas. Hence the painful region should be most carefully and repeatedly examined for the characteristic crepitation. The rub is rarely elicited in diaphragmatic and mediastinal pleurisy, until the inflammation spreads to the chest wall.

The tuberculous pleurisies, often apical, frequently come on insidiously and may be not suspected until revealed by the stethoscope. The history of intercostal neuralgia occurring periodically in the same location may be the only indication of chronic adhesions. Neuralgia associated with a daily rise in temperature should always arouse suspicion of tuberculosis. The leucocytes are more often increased in fibrinous than in serofibrinous pleurisy. Lord's statistics showed a leucocytosis of over 12,000 in nearly forty per cent. of his cases.

The diagnosis of an acute parietal pleurisy can ordinarily be made from the history and auscultation. Students are likely to mistake the vibratory sonorous râles of bronchitis or asthma for a pleuritic rub. There is also a muscular creaking sound audible over the scapular region that is confused with a true friction. This sound can at times be produced by passive movements of the shoulder blade during a cessation of respiration and is usually bilateral. The unusual types of pleurisy will be discussed in a later chapter.

Prognosis

The prognosis of a simple dry pleurisy is good, so far as the immediate infection is concerned. A considerable proportion will develop in later years signs of pulmonary tuberculosis. The outlook in metapneumonic cases is determined by the course of the lung lesion. Diaphragmatic pleurisy adds to the gravity of this group only as it intensifies two unfavorable factors in pneumonia, pain and dyspnea.

Treatment of Dry or Fibrinous Pleurisy

Rest in bed should be enforced regardless of the mildness of the symptoms. Complete rest may have a profound influence on the course of the disease. Pain is the one symptom demanding relief. Nothing is as effective as codein or morphin to control the early pains and cough. As the suffering becomes less severe, aspirin may be used. Strapping the affected side with adhesive plaster gives partial relief. Heat or cold, locally applied are both helpful, especially cold in the form of an ice bag. Strips of bandage chilled on a cake of ice and repeatedly applied to the tender area have a remarkable anodyne influence. The older physicians were much given to dry cupping over the seat of the pain and this procedure is well worth trial.

In diaphragmatic pleurisy strapping of the chest often increases pain by exaggerating the movements of the diaphragm. Pressure of a bandage about the abdomen is at times grateful to these patients.

2. Pleurisy with Effusion

Pleurisy with effusion is an inflammation of the pleura associated with exudate that may be serous, serofibrinous, seropurulent or hemorrhagic.

Etiology of Pleurisy with Effusion

It is well to keep in mind that all the clinical types of pleurisy are arbitrarily classified. A dry pleurisy more often than not will yield a few drops of serum to the exploring trocar. The terms employed are derived from the predominating elements found in the exudate, fibrin, serum, blood and pus. The factors determining the proportion of these elements are unknown or only partially understood. For lack of specific information we assume that the quality and virulence of the germ on the one hand and the individual reaction of the tissues on the other hand are chiefly concerned. But the type of inflammation that will be excited by a germ organism cannot be predicted. Thus the tubercle bacillus may cause a simple fibrinous, serous, hemorrhagic or purulent exudate. A pneumococcus pleurisy may terminate in the fibrinous, serofibrinous or purulent stage. The same variety of exudates prevails in pleurisies accompanying pneumonia and cancer.

The serous or serofibrinous effusion with an amount of fluid sufficient to give physical signs is generally of tuberculous origin. It is estimated that between seventy and eighty per cent. of all cases are tuberculous. Only rarely can the tubercle bacillus be recovered on a cover glass preparation or in the cultures, but inoculation of guinea pigs with the fluid causes death from tuberculosis in a high percentage of cases. Frequently too an effusion occurs in association with tuberculous lesions in the lungs and bronchial glands.

Serous exudates of pneumococcus origin are less common than the fibrinous. They have a greater tendency to become purulent than the tuberculous forms and are usually more localized. Occasionally streptococcus effusions remain serous, but all the pyogenic cocci show a disposition to pus formation. Acute rheumatic arthritis is of all general infections most often complicated with serous pleurisy. As a terminal condition in cancer, heart disease and nephritis, serous effusion frequently develops and may be confused with a transudate.

Symptoms of Pleurisy with Effusion

A patient may consult his physician complaining of shortness of breath, "rheumatic" pains in the chest, fatigue and loss of strength. Examination reveals a large accumulation of fluid in the chest. Such is the history of many cases of the tuberculous type. Rarely one sees the acute fulminating type, the pleurisy acutissima, which is characterized by a progressive accumulation of fluid. Dyspnea and cyanosis may be present, but not always to an alarming degree. Without warning the patient may become pulseless and die. Such a termination is avoidable by early aspiration of the fluid. Another group follows in the wake of pneumonia and provokes no other subjective symptom than increasing dyspnea. The temperature may remain elevated after the crisis and the pulse be accelerated.

Fever of moderate degree is common, but in no sense typical. As a rule the temperature rises during the secretion of fluid and becomes irregular or normal during absorption. More depends on associated or underlying conditions in influencing the temperature than the pleurisy itself. The course of a lung abscess, a tuberculous infiltration, an arthritis or a septicemia is likely to dominate the temperature curve. In the aged and in terminal pleurisies the temperature may remain subnormal throughout.

The acute pain, so characteristic of the dry pleurisy disappears as the effusion separates the membranes and gives place to diffuse muscular pains. Cough is not incited by an effusion *per se*. When cough is present, one looks for its source in a bronchitis. The sputum is surprisingly scant in the primary cases, but in secondary cases varies with the nature of the basic disease.

The respiratory rate, which we have seen is accelerated by the pain in dry pleurisy, becomes more normal during the accumulation of fluid, and cyanosis is less conspicuous than one would expect. The pulse responds to the influence of temperature and pain. Hence with the progress of an exudate the pulse may be slow. The arterial tension is maintained even when the exudate is large, although the volume of blood in the arteries is diminished. When, however, the fluid pressure is excessive the arterial tension falls.

Sweating is as characteristic of pleurisy as it is of articular rheumatism. The amount of perspiration is not dependent on the fever alone, but on other factors causing a vasomotor dilatation. The sweats are followed by sense of weakness and exhaustion.

The urinary output undergoes a decided diminution during the formation of the exudate and is further reduced by the sweating. A rise in the daily excretion often heralds the beginning of pleural absorption. Albuminuria and casts may be found in the urine, but seldom is the renal complication serious. Headache, indigestion and general weakness are commonly met with, resulting no doubt from the infection.

Physical Signs of Pleurisy with Effusion

The attitude of the patient may be suggestive as he attempts to leave the sound side free and usually uppermost if he lies on the side. As the effusion grows larger the upright posture is often assumed. Cyanosis and dyspnea are not conspicuous in small and moderate effusions. Irregularity of the pupils may be detected, the pressure on the pupillary fibers of the cervical sympathetic causing a dilatation of the pupil on the affected side.

The diseased side is less mobile than the healthy one, as shown by the limited motion of the shoulder. The interspaces are less concave than normally and under great pressures may bulge. Litten's diaphragm shadow is absent unless the fluid is small in amount or encapsulated in the upper portion of the cavity. One sees the apex impulse either to the left of the left nipple or to the right of the sternum, according to the side of the chest involved. In many instances where the effusion is large or the adipose layer is thick, the cardiac impulse is not visible; especially is this true of left sided pleurisies.

By placing the hands on both sides of the chest during deep respiration a difference in expansion may be observed. Also the cardiac impulse can be better located by touch than by sight. The most valuable sign elicited by palpation is pectoral fremitus. Three distinct zones can be differentiated under favorable conditions in an effusion of moderate size. The lowest zone transmits either a weak vibration from the spoken voice or none at all. The zone just above the fluid level gives an abnormally strong tactile fremitus, owing to the heightened transmissibility of the sound waves through the layer of relaxed or atelectatic lung. Over the upper zone the fremitus is normal. A thick fibrinous exudate also impairs the pectoral fremitus, so that the sign cannot be depended upon.

The value of percussion depends on careful, skillful technique as well as on proper interpretation of findings. At the beginning of the examination the sound side should first be gone over and the borders of the heart and liver determined. Loud, forcible percussion is often required in fleshy or dropsical subjects, but a light stroke is preferable in outlining the fluid level and is almost essential in small or circumscribed exudates. It is more convenient and satisfactory to have the patient in a sitting posture.

Dullness or flatness is the distinctive note over the effusion, but a considerable quantity of fluid (up to 500 c.c.) may be present without creating a noticeable change in the sound. Above the fluid the note is frequently hyperresonant or tympanitic, the so-called Skoda's resonance. The upper border of fluid follows a curved line, the S. curve of Ellis, which ascends from the anterior wall to the highest point in the posterior axillary space, then descends to its lowest level at the spine. The triangular space of Garland overlies the lung retracted toward the spine and is characterized by a hyperresonant note. When the effusion is large flatness extends over this space and over the upper portion of the chest. The region last to lose its resonance in massive exudates is the subclavicular space, which often remains tympanitic.

Effusion on the left side may fill Traube's semilunar space, giving rise to dullness or flatness instead of the normal tympany transmitted by gas in the stomach or colon. The sign loses much of its worth, because of the frequent presence of pleural adhesions or distention of the gastrointestinal tract with food.

Another region of some importance is the paravertebral triangle (Grocco's), a dull area at the base of the sound side of the chest posteriorly, the apex beginning at the upper level of the fluid and running diagonally downward to the base line. This is caused by a displacement of the mediastinum, the lower part yielding to a greater hydrostatic pressure than the upper part.

The displacement of organs is a most striking result of pleural accumulations and is recognized more readily by means of percussion than by inspection. Depression of the diaphragm may force down the liver so that its border may be found by percussion or palpation well below the costal edge. The spleen on the other hand is rarely displaced far enough to palpate. Displacement of the heart can be demonstrated by percussion in the absence of visible or palpable evidence. Dislocation of the posterior mediastinum has already been touched upon.

During the absorption of an effusion or after drainage, percussion shows a gradual return of the normal resonance. A favorable sign is the extension of resonance at the lower border during inspiration, which indicates the expansion of the lung with air. Demonstration of moveable dullness is almost pathognomonic of effusion. Unfortunately it is not a constant sign. It is obtained by locating the lowest interspace of resonance in the recumbent position; upon assuming an erect position this space becomes dull or flat. Numerous conditions interfere with the free shifting of fluid, notably adhesions, massive exudates and emphysema. It is most often observed in recent exudates of moderate size and in hydrothorax.

If one is so fortunate as to examine a pleurisy at the onset, he hears a pleural crepitation or a friction rub. As the fluid collects and compresses the lung, the vesicular respiratory sounds disappear and bronchial breathing is heard perhaps faintly and at a distance. Above the fluid moist râles may be audible. The voice sounds likewise become distant and altered in quality, according to the depth of fluid and condition of the lung. When the bronchi are clear and the retraction of lung slight, bronchophony or the more nasal egophony are present. In the presence of an excessive effusion the voice sounds are completely muffled. Bacelli's observation that the whispered voice is transmitted through a serous effusion, but not through pus, has not proved a trustworthy sign.

It has become almost a routine procedure in hospital practice to inspect the chest with the fluoroscope and take X-ray plates. The Roentgen picture requires experienced interpretation, as do other physical signs, but it has contributed greatly to accurate diagnosis.

Exploratory puncture of the chest for diagnostic purposes at one time was looked upon as a last resort when other methods failed. Today the procedure is considered a legitimate part of a careful examination. The information derived from puncture is: (1) the presence or absence of fluid; (2) the nature of the fluid, whether serous, purulent or hemorrhagic; (3) the bacteriological findings. Perhaps the most practical value is to determine if there is pus present, for if such is the case, drainage is usually essential to bring about the recovery of the patient. Often a puncture reveals consolidation where fluid was suspected, but no harm results even if the lung is entered.

Clinical Course of Pleurisy with Effusion

The clinical history of a serofibrinous pleurisy depends upon the nature of the exciting organism, the complication of other diseases, especially of the lungs, the resistance of the individual, and finally upon the treatment. A stormy onset with chills and fever is not necessarily unfavorable, for often absorption is rapid and complete. An extensive friction rub is usually followed by moderate effusion. Large effusions more often arise insidiously with a minimum of pain and often unaccompanied by friction sounds. The tendency in a simple pleural effusion of moderate size is to gradual absorption with more or less formation of adhesions between lung and pleura.

A massive effusion rapidly accumulating, pleurisy acutissima, is an immediate menace to life. The danger cannot be safely measured by the subjective symptoms or by the pulse rate, arterial tension, dyspnea and cyanosis. Sudden death may occur in these cases unless the fluid is withdrawn. The explanation of this collapse is rarely found in a pulmonary embolus. More often the necropsy fails to reveal any anatomic lesions. The most plausible theory is the one advanced by Rosenbach[15], that the increasing intrathoracic pressure reaches a point where obstruction to the vena cava takes place, resulting in a failure of blood flow into the heart.

The development of pulmonary tuberculosis after pleural effusion is not uncommon. This sequel may be explained either on the basis of a primary tuberculous infection of the pleura or a subsequent implantation of tubercle bacilli on a favorable soil.

The conversion of a primary serous effusion into pus is comparatively rare, occurring only 16 times in 1,185 cases reported by Lord. Serofibrinous exudates secondary to pneumonia on the other hand frequently change into empyema.

Diagnosis

The recognition of a primary serous pleurisy ordinarily presents little difficulty, because the physical signs are characteristic. The secondary cases need to be differentiated from pneumonia. Both effusion and consolidation give dullness and may exhibit bronchophony, but in the latter the viscera are not displaced. A thickened pleura is not always easy to distinguish from pleural effusion, and the two conditions may both be present. Exploratory puncture will clear up the diagnosis. Puncture is also necessary to definitely diagnose a small or circumscribed exudate. A tumor mass gives rise to flatness on percussion and its presence is often suspected for the first time after a dry tapping.

Treatment of Pleurisy with Effusion

The treatment of serofibrinous pleurisy may be considered as follows:

1. *Treatment of the Infection.*—The most favorable time for influencing the course of the infection is at the very onset. Rest in bed when promptly enforced may entirely modify the severity of the disease, both by securing relative quiet for the inflamed pleura and by increasing the resistance of the patient. A saline purge and a hot bath are advisable. The diet should be light. Specific remedies are lacking. Salicylates are thought to have some special action in rheumatic cases, but as they do not materially alter the progress of arthritis, they cannot be expected to materially influence the pleurisy.

2. *Symptomatic Treatment.*—The symptomatic measures of relief in the early stages are the same as in fibrinous pleurisy. The pain becomes less severe as the fluid increases and cough less troublesome.

3. *The Promotion of Absorption.*—Much has been written on the subject of preventing the secretion of fluids and encouraging their absorption after their accumulation in the chest. The measures employed for these purposes are the limitation of liquids in the diet and excessive elimination of fluids by the organs of excretion. Clinical experience bears testimony to the fact that these measures are often successful in transudates and rarely so in exudates. There is an essential difference in the two conditions that must be kept in mind in our therapeutic procedures. A transudate is non-inflammatory in origin and is brought about as a result of venous stasis, as occurs for example in cardiac decompensation. The pleural membrane is relatively normal, and responds to osmotic pressure. Therefore, a restoration of the circulation will favor absorption of the fluid. Likewise a depletion of the body fluids by means of a low liquid intake or abundant elimination, will tend to establish the flow of fluids away from the pleural cavity. On the other hand exudate is an inflammatory process, in which the

accumulation is produced by the secretory activity of the endothelial cells of the pleura. The pleura itself undergoes the changes of coagulation necrosis bringing about an occlusion of lymphatic and blood spaces. The pleura is no longer a membrane responding to osmotic influences. The cavity is temporarily walled off. Hence the measures above mentioned are no longer efficacious. Inflammatory secretion may take place even in dysentery when there is general dehydration of tissues. The pleural fluid may remain unchanged in quantity after purgation, free diuresis and sweating.

At the beginning of an exudate and at a late stage when the fibrin is undergoing digestion, the pleura may have a certain degree of permeability. There are also borderline effusions between transudates and exudates, in which the pleural membrane permits the exchange of fluids. Our therapeutic efforts may then be followed by positive results, but we cannot expect success in a majority of cases.

Restriction of liquids should not be enforced below a liter daily. The patient needs a diet of 2,500 calories to overcome the great weakness. The skimmed milk diet of Karell is not adequate to maintain the patient's strength. Hydragogue cathartics are of especial value at the onset. Epsom salts or the compound jalap powder are serviceable. Excessive catharsis should not be continued, however, for many days. Diuretics are often employed, caffein and theocin giving good results. Sometimes a spontaneous diuresis ushers in the period of absorption. Diaphoretics are not recommended because of the excessive sweating that naturally accompanies the disease. Cardiac stimulants are seldom indicated unless there is an associated myocarditis.

Iodides are deservedly losing their former popularity as absorption agents in pleural exudates. The known power of iodide is to bring about liquefaction and absorption of granulomatous deposits, such as the round cell infiltrations of syphilis and actinomycosis. In the rare instances where these infections invade the pleura the administration of iodides is rational. But there is no evidence that the drug has any influence on the ordinary exudates.

4. *Thoracentesis.*—Drainage of pleural effusions by thoracentesis has taken its place as the most important of all therapeutic measures for this condition. Practiced since ancient times by a few of the bolder spirits, the method was placed on a sound clinical basis by Laennec[16] and Trousseau[17] and introduced in America by Bowditch[18] and Wyman.

The indications for tapping formulated by Bowditch in 1852 cannot be improved upon today: "(*a*) When the chest is full in either acute or chronic cases; (*b*) when alarming dyspnea is present even if the quantity of fluid is small; (*c*) in all cases where absorption is slow."

The acute cases with rapid accumulation of a large amount of fluid have already been referred to. Trousseau became convinced of the necessity of immediate drainage in these cases to prevent death and coined the expression "indicatio vitalis." Most hospital clinicians can recall instances of effusion filling most of the pleural cavity, where tapping has been delayed on account of the absence of marked dyspnea and cyanosis, in which death unexpectedly occurred. When the fluid reaches the spine of the scapula behind or the level of the third rib in front, tapping should be carried out without delay. Fever is no contraindication. The fluid is likely to reaccumulate and require repetition of drainage. If one waits for a marked fall in blood pressure it may be too late to save the patient. Fortunately this acute type of pleurisy is rare.

Massive effusion of gradual development is much more common than the acute cases with very rapid accumulation. Occasionally a large effusion has been present for weeks or months before it is recognized. The constant pressure weakens the intercostal muscles, flattens out the diaphragm and destroys its function, and displaces the heart. Myocarditis may supervene as a result of chronic infection. Under these circumstances some unusual exertion, such as a paroxysm of coughing, sudden change of position or thoracentesis may throw the patient into collapse. Tapping is imperative in this group of cases and should be performed with as little shock as possible, and only a portion of the fluid should be withdrawn at the first operation.

Marked dyspnea and cyanosis are indications for thoracentesis regardless of the amount of fluid present. Encysted pleural effusions in the mediastinum or near the heart may cause symptoms out of proportion to the quantity of effusion. Under these conditions evacuation of a few ounces may bring considerable relief.

Failure of absorption or very slow absorption in effusions of moderate size calls for mechanical interference. Such an exudate is practically encysted and consequently may cause very little toxemia. The long continued presence of fluid, however, compresses the lungs and establishes firm adhesions which prevent the ultimate restitution of function. The patient is usually able to walk about and may complain only of shortness of breath on exertion. At the present time this type of pleural effusion is more neglected than any other, either because of a reluctance of the physician to operate or because of a mistaken diagnosis of pleural thickening. The results of drainage are always beneficial, although expansion is seldom completely restored. Exploratory puncture for diagnostic purposes has previously been referred to.

The Time of Preference for Operation.—In a typical case of pleuritic effusion, the fluid collects gradually for several days. During this period the endothelial cells are in a state of inflammation that keeps up a steady secretion, and it is probable that the presence of fluid separating the opposing membranes exerts a favorable influence on the inflamed surfaces. In other words the fluid serves as a protective covering as it does in an inflamed joint. Complete evacuation, therefore, is not advisable until the acute stage has passed, always excepting those conditions of urgency just discussed. The time of the quiesence of endothelial activity can be determined by the subsidence of fever and by the stationary level of the effusion. As a rule this takes place in a week or so after the initial symptoms. Tapping at this time of election is followed by less rapid and abundant reaccumulation of fluid, whereas very early evacuation is likely to result not only in a quick return of fluid, but in exacerbation of fever. The fever, however, does not justify a long delay in tapping after the exudate has become stationary, for in some instances the temperature actually falls after the drainage of the cavity.

Late tapping is especially recommended in pleural effusions associated with pulmonary tuberculosis. Königer[19] has emphasized the favorable influence of the exudate on the basal disease. The compression of the lung with atelectasis and the formation of fibrous adhesions are most desirable for promoting the healing of tuberculous infiltration. He advises the postponement of tapping for two weeks or longer. Then only a portion of the fluid should be taken away. When the effusion is small or moderate in amount, often it is advisable to let the fluid remain.

Posture of Patient.—The sitting position is rather more convenient for the operator as the patient can elevate the shoulders and spread the ribs apart, but it is decidedly bad for the patient. The upright position greatly exaggerates all circulatory disturbances, especially inducing cerebral anemia and faintness. The recumbent posture should be always preferred, the patient lying on the back or side with the shoulder raised on the side affected. The opinion is prevalent that evacuation is greatly favored by the upright position, but as a matter of fact, the rate of outflow is regulated more by the intrapleural tension and the action of the diaphragm and intercostal muscles than by hydrostatic pressure. There are complicating conditions which render the upright position obligatory, as in asthma, cardiac decompensation and pericarditis.

Aseptic precautions are necessary, as in all surgical procedures. The skin is painted with tincture of iodin or washed with soap and water followed by alcohol. Over the site chosen for puncture a saturated solution of phenol may be applied for twenty seconds and then washed off with alcohol, thus effecting a degree of anesthesia in addition to antisepsis. Novocain is usually used in old or nervous patients, but to be satisfactory must penetrate the deep sensitive intercostal tissues. Freezing the skin with ethyl chloride, a convenient anesthetic, serves to mitigate the cutaneous pain. General anesthesia is contraindicated in thoracentesis because it favors pulmonary edema and respiratory failure. All instruments should be sterilized and the hands of the operator thoroughly cleansed with soap and water and some antiseptic solution.

Site of Tapping.—The needle is inserted over the area of flatness as low as feasible. As a rule the midaxillary line in the sixth or seventh space is a desirable location because the muscular wall is thin and the intercostal spaces are wide. The seventh and eighth spaces near the angle of the scapula are particularly favorable to drainage of small effusions which may not extend to the front of the chest. A dry tap over one area should not be discouraging, for a thickened pleura may block the needle at any given spot. Often a second or third puncture at different locations is rewarded by a free flow. Encapsulated or interlobar effusions should be tapped where the physical signs and the X-ray photograph show the easiest approach to the fluid.

Technique of Thoracentesis.—The choice of instrument, needle or trocar, is largely a matter of individual preference. A hollow needle with a lateral foramen is more easily inserted and causes less pain than the trocar. The needle should be at least 2 mm. in diameter, as one with a smaller caliber is often occluded by a thick effusion. Occasionally the sharp point works an injury to the diaphragm or lung and as the lung expands may cause irritation of the visceral pleura. This irritation sometimes provokes a troublesome cough and exceptionally circulatory disturbances, unless the instrument is withdrawn.

A medium sized trocar with a smoothly fitting stilette is a safer instrument and by many preferred to the needle for therapeutic purposes. For exploratory tapping, however, when several punctures may be necessary, the needle is the instrument of choice. The finger of the left hand is pressed in the interspace selected and the upper margin of the lower rib well defined. The trocar is inserted inward and slightly upward over the upper border of the rib, thus avoiding the artery that runs along the under surface of the rib. Care should be taken not to scrape the sensitive periosteum and cause unnecessary pain.

When the pleural cavity is entered, the stilette is withdrawn and the fluid escapes. The flow is usually spontaneous, slowing with inspiration and increasing with expiration. Siphonage is the ideal method of evacuating fluid and should be practised wherever possible. To prevent the inward suction of air a rubber tube three feet long is attached to the canula and suspended in a bottle. In large effusions where the positive pressure is considerable and when the lung is expansile and the diaphragm is mobile, a large quantity may be obtained by siphonage alone. But in many cases the spontaneous flow ceases before the bulk of fluid is removed or even after a few ounces have escaped, because of a negative intrathoracic pressure. It then becomes necessary to aspirate.

In all methods of aspiration the tube leading from the canula is attached to a large bottle in which a partial vacuum is produced. The best apparatus is that of Potain, which creates a measured degree of suction by an exhaust pump. By turning a cock on the connection between the bottle and pump the negative pressure can be maintained. Occasionally the novice makes the wrong connection and pumps air into the bottle instead of exhausting it and this forces air into the chest. As a precaution the apparatus should first be connected and tested by sucking up sterilized water with the tube that connects with the trocar canula.

The rate of withdrawal should be slow. In hospital practice too often the patient's welfare is sacrificed by rapid evacuation to the convenience of the interne. Slow drainage favors the gradual expansion of the lungs, the replacement of the dislocated heart and the ascent of the diaphragm. Rapid evacuation causes engorgement of the pulmonary vessels and lowers the systemic arterial tension more than slow drainage. Faintness may ensue and terminate the operation prematurely. It is a good rule to use the minimum degree of suction and take plenty of time.

How much fluid should be withdrawn depends on the total quantity present in the cavity and the degree of suction required to keep up the flow. Not more than 1,500 c.c. should be taken away even under favorable conditions. If the exudate remaining is still considerable it is better to resort to repeated tappings in order to reestablish the function of the compressed lung.

Complications Attending or Following Thoracentesis

In the great majority of cases thoracentesis and drainage of an effusion is a simple procedure, not attended by any untoward symptoms. By many the operation is looked upon as of no more gravity than paracentesis of the abdomen in ascites, but there is an essential difference in the two conditions. In ascites the fluid is always under a positive pressure and drainage is accomplished by siphonage alone, whereas in pleural effusions the intrathoracic pressure may be zero or negative and aspiration is therefore required. Aspiration produces sudden and radical changes in the intrapleural tension which directly affect the pulmonary circulation, the action of the heart and the respiration. Most of the untoward symptoms occur toward the end of aspiration or within a few hours after the operation. Many of them can be prevented or mitigated by observing certain precautions to avoid too sudden or excessive alterations in the intrathoracic pressure. Too much emphasis cannot be laid on the fact that siphonage is comparatively free from these complications.

Pain is usually very slight after the trocar is inserted. Contact with the visceral pleura or penetration of the lung does not give rise to pain. When the trocar touches the diaphragmatic pleura, however, and this is not a rare occurrence, then pain is severe and referred to the neck or to the lower costal region. Partial or complete withdrawal of the needle is indicated.

Cough rarely occurs during the siphonage and during aspiration is most often observed after the withdrawal of a considerable amount of fluid. It is produced by irritation of the nerve endings of the vagus, probably as a result of pulmonary congestion. Contact of the trocar with the pleura is seldom the exciting cause. When the cough is persistent there is danger of tearing the lung and also of edema, so that it is best to withdraw the instrument. Morphin and atropin can be used with advantage before an evacuation.

Faintness is frequently encountered when the patient is sitting upright, especially in nervous individuals. For this reason the recumbent position is advisable. When faintness results from the pain of the puncture or from psychic disturbance, a dose of whiskey or aromatic spirits of ammonia will restore the circulation without interference with drainage. Another type of faintness not yielding immediately to stimulation is due to the excitation of the pleural or pulmonary nerves and occurs usually toward the end of drainage. This demands instant termination of the operation. The pulse is weak in faintness of both types. As a rule faintness develops when the systolic arterial pressure approaches 60 mm. of mercury, but the condition is generally transitory.

Hemorrhage may result from the wounding of the intercostal artery, but this is a rare accident, and can be remedied by applying a ligature. Pulmonary hemorrhage has been reported from penetrating consolidated lung tissue. In most of these cases a tuberculous cavity is entered and an artery wounded. Piercing the lung in lobar pneumonia is a common incident in exploratory puncture, but in the author's experience has seldom been followed by hemorrhage. Absolute rest and morphin are the best remedies if pulmonary hemorrhage occurs.

Infection of the exudate, converting the effusion from a serous to a purulent fluid, must be a very rare incident. A transformation of serum into pus may occur spontaneously in the pleurisies secondary to pneumonia. Moreover, empyema may be induced or hastened in certain instances by the withdrawal of serum, which Opie has shown is due to chemical and not bacterial influences.

Subcutaneous emphysema is an interesting complication, seldom serious, that occasionally arises from puncturing the lung. The air escapes along the needle track to the subcutaneous tissues and may spread over the chest and even to the neck. A localized edema is observed near the site of the tapping and a characteristic crackling sound can be both felt and heard. The condition lasts only a few days.

Pneumothorax of some degree can be demonstrated quite commonly a day or two after tapping. Frequently a little air is sucked into the cavity through loose fitting connections of the apparatus. A hyperresonant note over the upper level of the fluid arouses a suspicion of air, as the sound is more tympanitic than the Skodaic resonance. A shifting of this area and succussion sounds elicited by shaking the chest confirm the diagnosis. The admission of air during thoracentesis is not at all detrimental and may even serve a useful purpose so long as it does not exceed in volume the fluid withdrawn. No treatment is necessary and in a few days it is absorbed.

When, however, the pneumothorax results from a laceration of the pleura and lung the situation is serious, for the air is forced through the opening into the cavity until the wound closes

Edema of the lungs is a complication that may be fraught with grave consequences. It comes on generally toward the end of the evacuation or a short period afterward. Accompanying the edema is a cough with expulsion of an abundant pinkish frothy material, the so-called "albuminous expectoration." Dyspnea and a failing circulation may ensue with a fatal termination. The pathology of this condition is somewhat obscure, but an important etiological factor is the intense congestion of the retracted or atelectatic lung after the release of the compressing fluid. There is much reason also for accepting the theory of Cohnheim, namely, that the vessel walls of the compressed lung have undergone degenerative changes as the result of the compression affecting their nutrition so that the escape of blood is prevented.

The clinical conditions which induce pulmonary edema are the too rapid evacuation of fluid, the drainage of an excessive quantity and the employment of too much pressure during aspiration. The avoidance of these measures will go far to prevent the development of edema. There are, nevertheless, some instances of edema subsequent to drainage of a small effusion, even when siphonage alone is used.

The appearance of frothy expectoration is a signal for instant cessation of drainage. On theoretical grounds the introduction of a few hundred c.c. of air to replace a portion of the fluid removed should prove beneficial. Morphin and atropin have been the most successful of the many remedies employed for relief. Adrenalin is contraindicated because in experimental work it has often produced pulmonary edema.

Collapse and Sudden Death from Thoracentesis and Irrigation of the Pleural Cavity.—Sudden circulatory failure has been described in connection with edema and with the laceration of a pulmonary artery. But there are cases of sudden collapse and death in which no anatomical evidence of hemorrhage, edema or embolism can be discovered post-mortem. The reported cases are not numerous, but most clinicians of large experience have met with this unfortunate accident. Leichtenstern[20] states that the collapse may come on during aspiration, more often soon after aspiration or may develop during irrigation of the cavity with antiseptic solutions. He analyzes twenty-three fatal cases in the literature. Fox[21] reports twelve instances of fatal syncope, all without pathological lesions adequate to explain the complication.

The three fatalities described by Russell[22] were all in children with pneumonia. His explanation of the phenomenon is that the needle traumatizes the vagus nerve endings in the lung tissue, thereby setting up reflex disturbance of the heart. He considers the reflex as pulmonary rather than pleural, but other observers have usually failed to find a wounded lung in their necropsies. Moreover, by this hypothesis one cannot explain similar instances of collapse during irrigation.

Our interest in the subject was aroused by the collapse of a patient with pleural effusion within a few seconds after the puncture, when only a few ounces of fluid had escaped. The post-mortem showed no laceration of the lung, no hemorrhage or edema, and no lesion in the brain. Animal experiments show that although the healthy pleura is tolerant of irritation, the inflamed pleura may react to irritation, whether mechanical or chemical, by marked reflex circulatory disturbances. The pleural reflex may act on the cardio-inhibitory fibers of the heart through the vagus nerve endings or on the vasomotor centers through the sympathetic nerves. Clinically we have often observed a transitory fall in the arterial pressure coincident with the needle thrust, especially when much force is used. This is apparently due to a direct inhibition of the heart action and is usually quite transitory. The effect is exaggerated in the yielding chest of children or when the effusion is massive and the cardiac action already embarrassed. We also were able during thoracentesis, by scratching the pleura, to induce a fall in blood pressure even to the point of faintness.

Our conclusions based on these experiments were as follows: (1) Syncope occurring during the act of puncture is the result of direct cardiac inhibition. (2) Syncope during aspiration results from irritation of the pleural or pulmonary nerves, either by the trocar or by congestion. It is most common toward the end of the operation when the instrument is most likely to scratch the pleura and when the lung is most congested. (3) Syncope occurring within 48 hours after aspiration is probably due to the circulatory reflexes arising from congestion of the lungs. (4) Syncope during irrigation of the pleural cavity is the result of a reflex arising from the chemical irritation of the pleura.

The prevention of collapse should be directed toward these ends: (1) Avoid unnecessary force in penetrating the chest wall, especially in children and the debilitated. A dull trocar is often at fault. (2) Avoid irritation of the pleura as far as possible. See that the needle swings free and if it strikes the lung during respiration change the position. A trocar canula is less likely to irritate the pleura than a needle. (3) Regulate the aspiration in such a way as to produce the least congestion. Evacuate slowly, use only moderate suction and do not remove over 1,500 c.c. of fluid. (4) In irrigation of the cavity do not use irritating chemicals and see that the rubber drainage tube does not scratch the pleura.

Therapeutic Introduction of Air after Aspiration.—The harmlessness of air accidentally entering the pleural cavity during thoracentesis has already been commented upon. It has been suggested by Achard[23] and others that sterile air can be introduced advantageously after evacuation to partially replace the fluid. By this method he succeeded in drawing off three or four liters with safety. A more important purpose in substituting an air cushion in place of the heavier effusion is to avert the excessive congestion of the lungs. The air is absorbed much more rapidly than the fluid and allows a gradual expansion of the retracted lung. It seems rational to suppose that edema and circulatory disturbances would be mitigated by this procedure. I have never seen infection take place from introducing air filtered through cotton. The amount of air admitted should be relatively small, never exceeding one third of the quantity of fluid evacuated.

End Results.—A perfect recovery means complete replacement of dislocated viscera, recovery of normal lung expansion and free mobility of the diaphragm. In favorable cases the fluid ceases to accumulate after one or two tappings and the lung recovers its full function. When, however, thoracentesis is long delayed, adhesions have formed to such an extent that the affected lung only partially expands. Much may be accomplished in the after treatment by the daily practice of breathing exercise, by active out-of-door life and good nourishing food. For years afterward, however, one may expect to find over the affected side relative dullness and more or less impairment of the vesicular respiration.

3. EMPYEMA

Empyema is a pleurisy with purulent effusion.

Etiology

The exudate may be purulent from the beginning, but usually it starts as a seropurulent effusion and gradually acquires a thicker consistency as the pus cells increase. The pneumococcus and streptococcus are the common etiological germs found in the exudate. According to most observers the pneumococcus is the causative organism in about half of all cases in hospital practice. Lord, in his series of empyemas, found streptococcus in 39.4 per cent., pneumococcus in 20.4 per cent., staphylococcus in 3.6 per cent., and mixed infections in 16 per cent. The pus was sterile in 18 per cent. and many of this group were tuberculous. But during the recent war period the statistics show a predominance of the streptococcus. The great epidemics of measles, influenza and streptococcus pneumonia were associated with an overwhelming proportion of streptococcus empyemas. The tubercle bacillus is not infrequently responsible for a purulent exudate, especially in the type where no organisms are present. Many tuberculous pleurisies become purulent after the secondary invasion of pyogenic cocci. Occasionally the influenza bacillus, staphylococcus, actinomyces and Friedlander's bacillus are found in the pus. Empyema is generally a complication of some pulmonary inflammation. Lobar pneumonia, bronchopneumonia, abscess of the lung and tuberculosis are the chief primary diseases. In military practice penetrating wounds of the chest contribute a fair share of the cases.

Pathology

Associated with lobar pneumonia there is nearly always a thick fibrinous exudate, in which leucocytes and pneumococci abound. Empyema often springs from this soil and the pus is thick, creamy and has a peculiar greenish color. The pus in streptococcus and tuberculous empyema is thinner and contains fewer formed elements. In actinomycosis the pus is thick and in it are found the characteristic granules.

A purulent exudate in the chest works far more damage to the viscera than a serous effusion. The intense inflammation of the pleural surfaces brings about early organization of the fibrinous exudate and the formation of thick, firm adhesions. After a time the retracted lung is incapable of expansion even when the pressure is removed by operation. Likewise the adhesions to the mediastinum tend to permanently fix the heart in its displaced position. According to Norris and Landis[24] prolonged compression of the lung by pyothorax is one of the common causes of localized pulmonary fibrosis. Similar changes take place in the pleural covering of the diaphragm, leading to loss of mobility and deformity.

Spontaneous absorption may take place in small collections of pus. When a large accumulation is left to nature, septicemia ensues. Exceptionally, pus may be so completely walled off that absorption is slow, and the patient lives to develop amyloid changes in the kidney, liver and spleen. A neglected empyema occasionally secures an outlet by perforation through the lung, draining into the bronchial tubes or through the chest wall.

Symptoms of Empyema

During the course of a lobar pneumonia the presence of pus is first suspected by the persistence of fever after the crisis seems to have passed.

The morning temperature may fall, but day by day the evening temperature is high. Dyspnea may have disappeared, but the pulse rate remains rapid, the patient acquires a pale sallow color, perspires freely and loses weight. The streptococcus empyemas complicating influenza pneumonias have an earlier onset and cannot be readily apprehended by the symptoms, as they are practically the same for both conditions.

Leucocytosis is the rule in pneumococcus empyema, and in streptococcus empyema, following measles or abscess of the lung. In the influenza bronchopneumonias, however, a normal or low leucocyte count is present in the majority of cases and the development of empyema seems to have no constant influence on the white corpuscles.

Physical Signs of Empyema

The detection of pyothorax is more difficult than that of serous effusions, for the latter is usually a primary condition, while the former is generally associated with some form of inflammation of the lung. A simple empyema exhibits physical findings very similar to those of serous effusion. But the numerous cases of metapneumonic empyema give rise to the most protean manifestations, owing to the fact that the pus is superimposed upon a profoundly altered lung tissue. The early recognition of empyema demands the greatest skill, study and experience on the part of the clinician. A final diagnosis is not always possible by the older methods of examination. The X-ray has proved of great assistance in the localization of pus, especially when it is encapsulated or situated between the lobes. Exploratory puncture must also be looked upon as one of the legitimate and most valuable diagnostic procedures.

The appearance of the patient, after the empyema has been present for some time, is that of sepsis. The affected side is more or less crippled in its respiratory movements and the diaphragm shadow cannot be seen. Bulging of the interspaces with slight edema of the chest wall can often be demonstrated, especially in children and thin individuals. When the abscess points there is a localized bulging and later a fistulous opening, the so-called "empyema necessitatis."

Pulsating empyema is not a rare condition and is nearly always on the left side (Sailer[25]). The cardiac pulsations are transmitted through the adjacent fluid. Displacement of the apex impulse is common with these larger effusions. A late manifestation of chronic empyema is clubbing of the fingers which according to Norris disappears after the pus is evacuated.

By the sense of touch the levelling of the interspaces and the abnormal position of the apex beat may be perceived. Tenderness to pressure over the inflamed area is a sign of value and is attributed to a neuritis of the intercostal nerves. Empyema tends to impair or to destroy the tactile fremitus.

There is no essential difference in the percussion note over an exudate of serum and of pus, except possibly that the flatness is more marked in the latter. As in serous effusions the vesicular sounds are usually lost and the voice sounds distant and diminished in intensity. But the frequency of bronchophony over areas where the lung is adherent to the chest wall makes one conservative in the interpretation of auscultatory evidence. It is often impossible by means of the stethoscope to differentiate between consolidation and empyema. Baccelli's sign, the transmission of the whispered voice through serous fluid and failure of transmission through pus, has proved to be unreliable.

Diagnosis of Empyema

The signs of pleural effusion have already been described. The purulent character of the exudate is apprehended by the development or continuance of fever, anemia and sepsis. Coming in the wake of croupous pneumonia, empyema is commonly mistaken for delayed resolution of the lung, a presumption that can only be justified after repeated efforts have been made to eliminate the presence of pus.

The Roentgen ray has become established as a method quite as valuable as percussion and auscultation in the diagnosis of empyema. Its peculiar field of usefulness is in the localization of encapsulated pus pockets that are too deep for recognition by sound variations. These atypical forms will be described separately.

Time and experience have shown that the diagnosis of empyema must be determined not by any pathognomonic signs, but by a correlation of the evidence obtained by all these methods. Even puncture may be misleading, for a dry tap does not exclude the presence of pus.

Military Experience With Empyema

During the war empyema assumed the rank of first importance among medical problems. The great prevalence of the disease, its unique and variable character and its heavy contribution to mortality have made it the subject of numerous studies and make necessary a somewhat detailed description. For the voluminous literature on the subject the reader is referred to Progressive Medicine[26], the Reports of the Empyema Commission[27], and to the article of Vaughan[28].

Empyema complicating the ordinary croupous pneumonia presented in the main the same clinical picture with which we are familiar in civil practice and needs no special comment. The unusual features of the empyemas in military service were due to the unprecedented epidemics, first of measles, second of streptococcus infections and finally of influenza. Bronchopneumonia in all three outbreaks was the prevailing pulmonary complication; exhibiting the greatest variety of anatomical lesions. Associated with these pneumonias were empyemas equally atypical in location, onset and in their clinical course. The pus was almost always caused by the streptococcus, and the variations in type were attributed largely to the factors of virulence as influenced by the initial infection and by the susceptibility of the host.

During the first years of mobilization measles and streptococcus infections of the respiratory tract were rife. Three periods stand out as distinctive in the virulence of the lung and pleural complications.

The first period from November to January 1918 inclusive represented the maximum intensity of the infection. Following measles the patient developed dyspnea, fever and cyanosis. The lung became edematous, and a serous or seropurulent fluid escaped into the pleural cavity. This effusion abounded in streptococci and the organisms were present in blood cultures. A fatal termination often supervened before the lung was consolidated and before the exudate was purulent. Aspiration or surgical incision had little or no influence in retarding the fulminating infection and even may have been detrimental. Some patients survived this stage and developed true consolidation and empyema as well as abscess of the lung. Surgical intervention was then indicated, but might fail to drain all the pus pockets.

The second period during the winter months showed a less virulent and less stormy infection. Consolidation and abscess of the lung were common, and the effusion, at first serous, became thick and purulent after an interval of several days. Metastatic effusions often developed in the pericardium, and joints and multiple abscesses in the skin. The mortality was still formidable, but far less than in the first period.

The third period in the spring months was milder in every respect. Empyema was slow in its formation and was responsive to treatment by aspiration and incision. The infection seemed to have become attenuated and most patients survived.

Empyema following influenza was a feature of the great epidemic in the fall of 1919. Here again we saw at the beginning of the outbreak an infection of overwhelming virulence, in which the patient was likely to die before consolidation was advanced and before the streptococcus effusion had become thickly purulent. Aspiration or incision both failed to retard the unfavorable progress of the infection. A few weeks later, the influenza virulence underwent a transformation and the intoxication was less severe. There was time for the gradual pneumonic progression from congestion to consolidation, and for the leisurely conversion of the seropurulent pleural exudate into pus. Measures for the removal of the fluid, whether aspiration or thoracotomy, now were helpful.

Treatment of Empyema

A consideration of the phenomena of virulency just described readily explains the heated discussions for and against early tapping and the relative merits of thoracentesis and thoracotomy. The great divergence of mortality statistics, usually ascribed to this or that method of treatment, is in reality due to varying stages of virulency of infection. In hospitals where the same method was followed continuously, the mortality was high in the early virulent period and low in the later mild periods. The condition of the patient is quite as important as the disease in deciding upon therapeutic methods.

Early thoracotomy in these cases certainly is a dangerous practice, because the patient is in no condition to undergo the shock. Aspiration with the needle or trocar can be repeatedly performed with very little discomfort to the patient. In less virulent infections aspiration should be employed until a considerable degree of immunity from the pneumonia has taken place. Then thoracotomy is advisable if evidence of pus persists.

Pneumococcus empyemas of small amount occasionally are well drained with complete recovery by aspiration alone, but in the vast majority of cases the treatment should be turned over to the surgeon. Consultants and chiefs of service spent much of their time in overcoming the hesitation and timidity of ward surgeons in performing pleural puncture as a matter of routine in all doubtful cases. Even with this avowed policy a surprisingly large number of empyemas were first discovered at necropsy.

Pus Pockets.—Streptococcus infections are prone to form multiple pockets of pus in the pleural cavity as a result of adhesions. These pockets present great difficulties in drainage, requiring aspiration at different localities, as they are often not confluent. After thoracotomy the operator may be compelled to break up the adhesions to establish free drainage. Staphylococcus infections are inclined to cause multiple lung abscess with extension to the pleural cavity. A favorite site for these pockets is near or under the sternum (Stone).

The surgical treatment of empyema does not properly belong to this chapter, but we may be permitted to touch on one or two questions of surgical procedure. The Empyema Commission of the United States Army advises against early operation in streptococcus empyemas, "because of the danger of lung collapse from pneumothorax; because of the danger of producing a blood stream infection from absorption of streptococci from the fresh wound surfaces; and because of the desperate state of the patient."

As soon as the diagnosis is made they advocate aspiration every other day until the pus is too thick to run, then thoracotomy if the condition of the patient permits. Graham and Bell[29] have shown that an open pneumothorax constitutes a great risk when there are no adhesions to wall off the mediastinum and thus protect the opposite lung from compression. Hence in acute pneumonia or an early streptococcus empyema where such adhesions are not yet formed, thoracotomy with the establishment of an open thorax carries with it an unwarrantable danger. Aspiration is indicated until the conditions become favorable.

Irrigation of the chest cavity following operation has been both praised and condemned by surgeons. Dakin's solution has seen used quite extensively with varying results. It is well in this connection to call attention to the accidents sometimes arising in the course of irrigation. Convulsions have been described by Weill[30] with syncope. Janeway[31] observed a transitory paralysis on two occasions while injecting a solution of hydrogen peroxide. Following the introduction of a two per cent. solution of formalin and glycerin Billings[32] reports a case of collapse and death. One case of sudden death while introducing Dakin's solution has come to our attention. Fatal syncope has followed the rather forceful adjustment of the drainage tube.

The cause of this syncope has been explained by Lewis and the author[8] as a circulatory reflex arising from irritation of the sensitive, inflamed pleura. Pressure of the fluid could not be responsible, because the amount of fluid introduced was often trivial. Nor are the chemicals used necessarily toxic. We found that the irritating character of the solution was a definite factor. Thus iodin solution never affected the arterial tension, while hydrogen peroxide and formalin did lower the pressure in experimental animals. Of course, the pleural membrane in empyema is usually protected by a fibrinous exudate and chemical irritation is thus avoided. But the exposure of a denuded pleural surface to chemical irritants affords an opportunity for circulatory reflexes that are fraught with danger.

Results of Treatment in Empyema.—True prognosis so intimately depends upon the associated diseases and the resistance of the individual that no generalizations can be made. A few of the special conditions that determine the course of the disease may be touched upon.

Empyema in children in the first two years of infancy has a high mortality. Later on in childhood, however, the disease is more amenable to treatment and ends in recovery more often than it does among adults. This favorable course is explained by the fact that most empyemas of children are metapneumonic and caused by the relatively benign pneumococcus. Thoracentesis in children requires careful manipulation, because the small and yielding chest is easily compressed and the circulation easily disturbed. A sharp trocar or needle and the use of ethyl chloride spray over the skin will materially lessen the shock.

Pneumococcus empyema responds the most favorably to treatment. Small exudates following lobar pneumonia are often absorbed after one or more tappings. The larger exudates are good surgical risks and most of them recover. Streptococcus empyema runs a more insidious course. It seldom yields to treatment by aspiration alone. Thoracotomy often fails because of the tendency of the pus to gather in multiple pockets, which are often overlooked by the surgeon. Tuberculous empyema offers a bad outlook. Drainage by the aspirating needle may mitigate, but does not cure. Thoracotomy is indicated only when the exudate is small and the strength of the patient is reasonably good. The operation is likely to light up the tuberculous lung and hasten the end. In the presence of advanced pulmonary lesions, the clinician's endeavor should be to give symptomatic relief and this is often accomplished by aspirating a portion of the pus.

Empyema in actinomycosis is generally secondary to a lung infection. The pus is destructive of tissue and tends to perforate the chest wall. The pus contains small granules which show under the microscope the characteristic threads and club-shaped bodies. Free evacuation should be performed and iodide of potash administered internally. 10 to 30 grains (0.65 to 2 gm.) a day may be given for a few days. In spite of treatment these cases tend to form chronic suppurating sinuses and to terminate in amyloid degeneration of the viscera. Putrid empyema is a purulent exudate with a foul offensive odor. The smell is produced by the action of gas producing organisms, mostly of the anerobic group. Often there is a mixed infection and free gas may be demonstrated in the pleural cavity. The prognosis is bad even with the best surgical measures.

4. Atypical Forms of Pleurisy

The preceding pages have been devoted to the discussion of the commoner types of pleurisy, which are comparatively easy to diagnose and treat. There are other types of pleurisy with or without exudate that in the aggregate are numerous and that are often baffling to the clinician. A localized process near the diaphragm, the mediastinum, the pericardium or between the lobes excites symptoms and signs which are often distinctive and quite different from the classical text-book descriptions. Hence it is desirable to consider these atypical forms at some length.

(1) *Diaphragmatic Pleurisy*

The symptoms and signs of diaphragmatic pleurisy are entirely unlike those of parietal pleurisy and are often characteristic. By most writers it is treated as a rare type; but in our experience it is of frequent occurrence and is either overlooked or the findings are misinterpreted. Diaphragmatic pleurisy may begin and end in a small localized area, giving no auscultatory signs whatever of its presence. Its recognition then depends on the location of referred pain and on the X-ray revelation of adhesions between the diaphragm and lower lobe. The condition is most commonly found, however, in pneumonia of the lower lobes and in extensive pleurisy of the lower thorax. In a series of 93 cases including those previously reported by the author, 57 of the patients had a lower lobe pneumonia with pleurisy, and 36 had pleurisy alone. In 47 the pleurisy was situated on the right side, in 35 on the left, and in 1 was bilateral. The diagnosis was in most instances made evident by physical findings in the thorax, in 8 instances confirmed by autopsy, and in 6 instances abdominal disease was excluded by exploratory laparotomy.

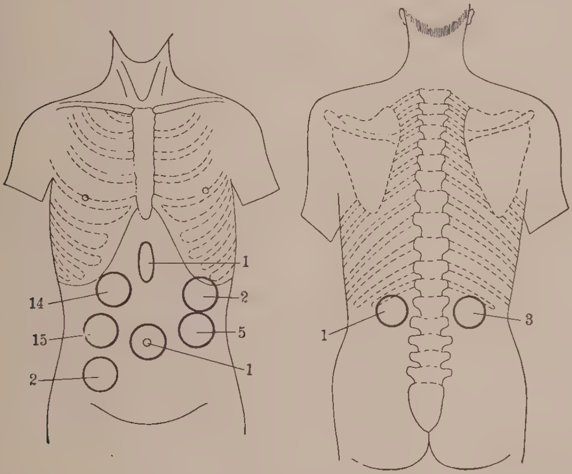

FIG. 4.—Points of maximum pain and tenderness in abdomen and back occurring in 93 cases of diaphragmatic pleurisy.

Pain referred to parts distant from the seat of inflammation was the outstanding symptom in these cases. Referred abdominal pain was present in 64 cases, in all cases involving the upper quadrant (7 to 10 dorsal segments), and in 27 cases the lower quadrant as well (10 to 12 dorsal segments). Bilateral pain in the belly was noted four times. The pain was usually spontaneous and with it was tenderness to pressure. Hyperesthesia and hyperalgesia of the skin were almost constant and showed a decided tendency to follow band-like areas corresponding to different spinal segments. Over this sensitive area the musculocutaneous reflexes were exaggerated and often the wall remained in a state of rigidity.

The maximum point of pain and tenderness to pressure was especially studied (Fig. 4). This point was located: (a) In the gall bladder region, 14 times. (b) Lateral to and slightly above the navel, 20 times. (c) Near McBurney's point, 2 times. (d) Over the navel, 1 time. (e) Midepigastrium, 1 time. (f) Splenic region, 2 times. (g) Lumbar region, 4 times.

Referred neck pain occurred in 62 cases, or in a little more than two-thirds of the total. The pain was located by the great majority of patients along the trapezius ridge, occasionally over the shoulder cap and in the supraclavicular space (Fig. 5). All of these areas are supplied with sensory nerves from the third and fourth cervical spinal segments. The pain was usually spontaneous and of sharp stabbing character, always well localized by the patient with the tip of his finger. Pressure over this point was often very painful. The skin and subcutaneous tissues in the immediate neighborhood showed the same hyperalgesia and hyperesthesia as were found over

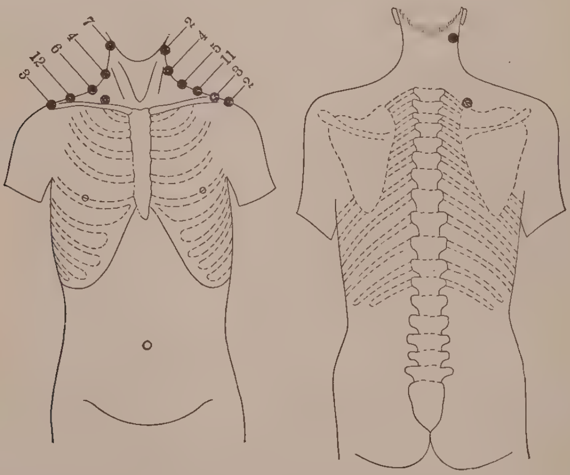

FIG. 5.—Points of maximum pain and tenderness in the neck region occurring in ninety-three cases of diaphragmatic pleurisy.

the abdomen, but the point of maximum pain and tenderness in the neck was sharply localized, and more constant. The exact locations of maximum pain points in the neck are illustrated in Fig. 5.

Kelly and Weiss[33] found a common area of tenderness over the twelfth rib posteriorly, occurring seventeen times in twenty-two cases of diaphragmatic pleurisy.

Factors Influencing Pain in Diaphragmatic Pleurisy

The appearance of referred pains in the abdomen or neck was generally early in the course of the disease. More often abdominal pain preceded the neck pain when both were present. The duration of the pain and tenderness varied in much the same way as in parietal pleurisy. Sometimes the pain disappeared after a few hours; as a rule it persisted one to three days and occasionally over a week. The pain was nearly always induced or aggravated by cough and deep inspiration, especially during the acute stage.

Measures limiting the excursion of the diaphragm on the affected side, such as lying on the painful side or tight pressure of an abdominal band often gave relief. Some patients secured ease by lying doubled up on the affected side with the shoulder held down by a pillow.

The abdominal pain was associated with a maximum point of pain and tenderness, far more frequently on the right than on the left side. Such a point was observed in 31 out of 47 cases on the right side, or 66 per cent.; while it was noted in only 7 out of 35 cases on the left side, or 20 per cent. In contrast to this disparity, the neck pain occurred with almost equal frequency on the two sides. Tenderness of the phrenic nerve, a symptom emphasized by many writers, was found in but one case and that was doubtful. Vomiting was present in 17 cases and was often responsible for a mistaken diagnosis of abdominal inflammation. Hiccough, another symptom supposed to be common in diaphragmatic pleurisy, was noted in only 6 cases, being unusually severe, however, in three.

Differential Diagnosis of Diaphragmatic Pleurisy

Appendicitis was incorrectly diagnosed in 9 cases. Two of these were operated upon and the abdominal viscera found to be normal. Cholecystitis was diagnosed in 8 instances, 2 of which came to laparotomy without discovering any pathological condition of the gall bladder or the neighboring structures. Ulcer of the stomach with perforation was twice diagnosed and once operated upon without discovering any lesion in the belly. Liver abscess was diagnosed in two patients. One was opened up with negative results. The other mistaken diagnoses included one instance each of peritonitis, renal calculus, infectious lumbago and brachial neuritis.

The main points of differentiation between diaphragmatic pleurisy and inflammation of the abdominal viscera are as follows:

1. In referred pleural pain the skin and muscles of the abdomen are more sensitive to pain and touch than in visceral disease. This is best elicited by pinching of the wall and scratching of the skin.

2. In referred pain the cutaneous reflexes are more lively than in visceral disease as a rule.

3. Deep pressure with the flat surface of the fingers is well borne in referred diaphragmatic pleural pain, while it elicits a dull deep pain when applied over the inflamed organ, *e. g.*, an appendix or gall bladder.

4. Evidences of respiratory infection are usually present in diaphragmatic pleurisy, such as cough, expectoration, herpes of lips, sore throat, high leucocytosis, rapid respiration, etc.

5. Appearance of a sharp, definitely localized pain in the neck on the same side as the abdominal pain often reveals the true condition, since it points to irritation of the phrenic nerve.

6. The referred pains in the neck and abdomen are usually induced or aggravated by cough and deep inspiration.

7. Nausea and vomiting are more constant in visceral abdominal inflammation, but may occur and be very pronounced also in diaphragmatic pleurisy.

8. The X-ray may show a deformity of the upper surface of the diaphragm from pleural adhesions.

9. Hiccough is not a common symptom in diaphragmatic pleurisy, contrary to the current belief. It was present only 6 times in our series of 93 cases. It is more often seen in visceral diseases of the abdomen than in diaphragmatic pleurisy.

(2) *Subphrenic Inflammation*

In the study of pain distribution from subphrenic inflammation, we are greatly handicapped. The opportunities for experimental irritation of the under surface of the diaphragm in human beings are rare. Moreover, the existence of abdominal pain in the course of subphrenic inflammation may be properly attributed to associated inflammation of the abdominal viscera. Only in those cases in which definite, sharply localized pain and tenderness develop in the neck or shoulder region, can we be sure that the diaphragm is involved. We have observed six cases of subphrenic inflammation exhibiting neck pain, three on the left and three on the right. The painful point is in every respect identical with the referred pain in diaphragmatic pleurisy.

The nerve supply of the peritoneal covering of the diaphragm is probably the same as that of the pleural surface, that is to say, the lower intercostal nerves supply the outer margin, and the phrenic nerves supply the central portion. Hence it is impossible by the pain alone to differentiate between supraphrenic and subphrenic inflammation. The symptomatology and physical findings must also be considered in order to establish the diagnosis.

(3) *Interlobar Pleurisy*

A pleural exudate may become encapsulated at any point along the surface of the pleura. These pockets when located near the chest wall can often be discovered by auscultation and percussion and readily explored by the needle. An encysted exudate situated between the lower lobe and diaphragm is not so easily detected, although the referred pain may give a clew. A pocket of exudate localized between the lobes is more common than our medical statistics would indicate, since it is often first revealed by postmortem. Fluid never becomes encysted unless the pleura is inflamed, so that the condition is unknown in simple hydrothorax.

Symptoms of Encysted or Interlobar Empyema.—A chill and fever may mark the onset, or the exudate may be a sequel of pneumonia or abscess of the lung. When the effusion is purulent, there is cough, intermittent fever, sweating and prostration. Pain may be present from involvement of the parietal pleura, but does not arise from the interlobar coverings. A leucocytosis is often present. The true nature of the septic condition may be first suspected when the patient expectorates a quantity of pus.

Percussion often yields dullness over the region of fluid, and auscultation may elicit moist râles from the contiguous congested lung. Sometimes there is a bronchial element to the breathing or a suppression of the vesicular murmur. From the nature of the symptoms and signs an abscess of the lung or tuberculosis with cavity is suspected.

The X-ray is invaluable in locating the fluid. The accompanying cuts from the paper of Sampson, Heise and Brown[34] show the contact surfaces between the lobes and make it possible to interpret the peculiar contour and characteristic location of the shadows in the Roentgen photographs. (See Figs. 6, 7, 8, 9).

By the aid of the X-ray pictures the clinician is enabled to make exploratory puncture at the most favorable spot. The needle may have to be

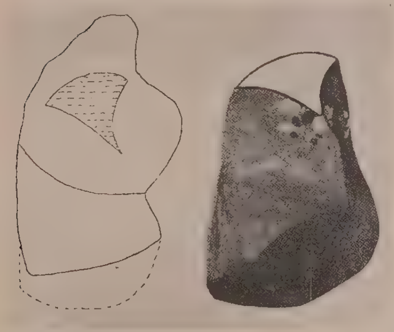

FIG. 6. — Shows contact surface (dotted area) between the upper and lower lobes, with accompanying photograph. From Sampson, Heise and Brown, *Report of Trudeau Sanatorium*, 1918, p. 677.

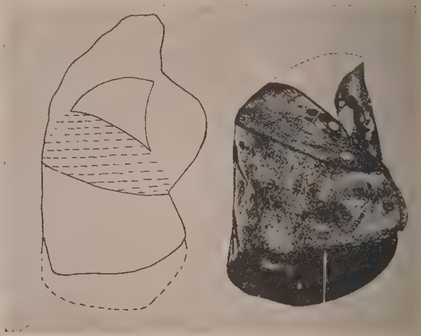

FIG. 8.—Shows contact surface (dotted area) between the upper and middle lobes, with accompanying photograph. From Sampson, Heise and Brown, *Report of Trudeau Sanatorium*, 1918, p. 678.

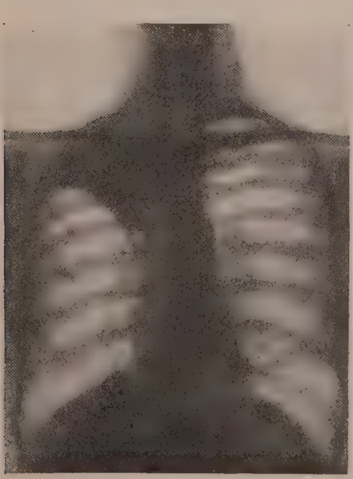

FIG. 7.—Interlobar Pleurisy between upper and lower lobes. From Sampson, Heise and Brown, *Report of Trudeau Sanatorium*, 1918, p. 677.

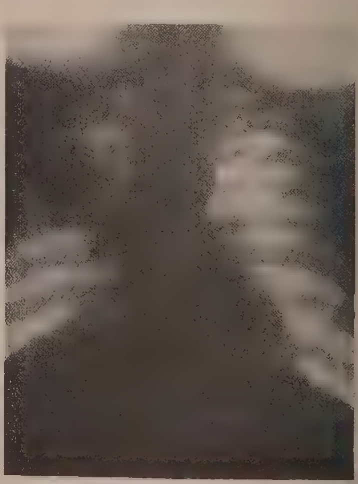

FIG. 9. — Illustrates an Interlobar Pleurisy between the upper and middle lobes.

inserted to an unusual depth. When pus is found in any quantity, the surgeon should immediately secure thorough drainage by thoracotomy and the insertion of a rubber tube. Surgical interference however is best delayed until the fluid has been definitely located by the needle.

(4) *Mediastinal Pleurisy*

A dry fibrinous exudate in the region of the mediastinum is of no special importance and cannot be recognized clinically. It is only when there is an encapsulated exudate present that the diagnosis is desirable or possible. A convenient anatomical classification is that employed by Frick[35] in his excellent article on the subject, which in substance is quoted.

1. Pleuritis mediastinalis anterior sinistra, in which the effusion is located in front of the left pulmonary peduncle. The fluid may extend along the upper mediastinal pleura or downward to the diaphragm and outward to the parietal pleura. It seldom extends to the posterior mediastinum. The symptoms that are distinctive are pain under the sternum or between the sternum and nipple. Dyspnea is proportionate to the pain. Cyanosis is conspicuous only in the large effusions. The chief physical signs are flatness beyond the cardiac dullness, obscuration of the apex beat, and occasionally a bulging of the precordium. The condition is usually confused with pericardial effusion or a suppurative mediastinitis. The X-ray may be of assistance by revealing a shadow contour unlike that of pericarditis.

2. Pleuritis mediastinalis anterior dextra may give rise to substernal pain similar to that described in the sinistra, but the pain tends to extend to the right nipple. Cyanosis is more frequently encountered on the right because of the pressure on the superior vena cava. Flatness is present a varying distance to the right of the sternum.

3. Pleuritis mediastinalis posterior is always situated on the left or right of the mediastinum, but the manifestations are the same in either case. The process may give no symptoms whatever except those of septic absorption. In other instances the effects of pressure on various structures are seen: paroxysmal cough from pressure on the vagus nerve; dyspnea, edema of the larynx and hoarseness from pressure on the trachea; dysphagia from pressure on the esophagus; dilatation of the thoracic veins from pressure on the azygos veins. Pain is exceptional, although there may be a region of tenderness near the spine. The posterior location is more common than the anterior.

A typical case of the author's is shown in Fig. 10. Following a bronchopneumonia of the left lower lobe, the patient ran a septic temperature with a marked leucocytosis and a daily expectoration of a moderate quantity of sputum containing pus cells and pneumococci. The tentative diagnosis of unresolved pneumonia was abandoned after the restoration of normal lung findings. There was no pain, but slight tenderness over the lower thorax near the spine. The X-ray showed a penumbra about the heart shadow from the antero-posterior view (Fig. 10). The lateral exposure marked out the outline of a bulging mass close to the spine and quite distinct from the pericardium (Fig. 11). Upon this evidence a needle was inserted in the eighth space posteriorly inside the scapular line and directed forward and toward the median line. A few drops of thick pus were obtained on deep penetration. The surgeon incised the wall at this point, followed the needle track with long hemostatic forceps, dilated the opening and inserted a rubber tube. Drainage of pus continued for several days until the leucocytosis disappeared and the X-ray showed no mediastinal shadow. Recovery was complete.

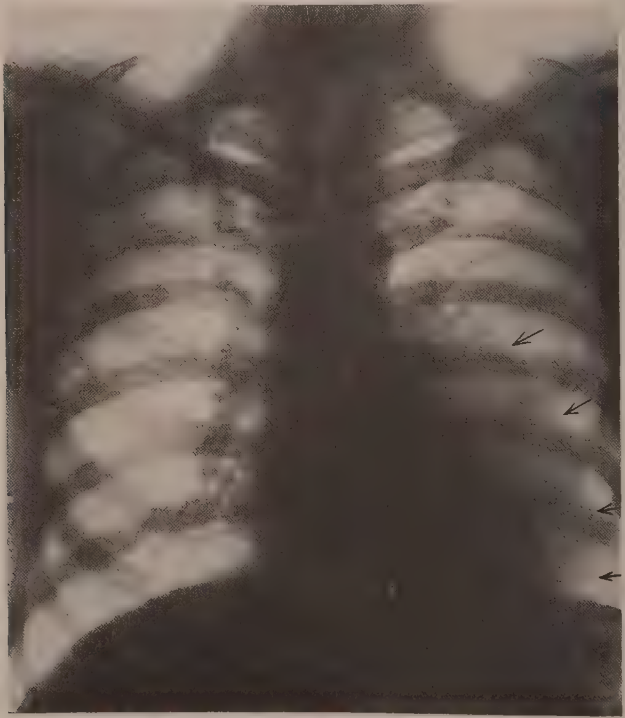

FIG. 10.—Left sided Mediastinal Abscess following Pneumonia. (Antero-posterior view.)

In all varieties of mediastinal exudates the X-ray is indispensable. Fluoroscopic examination will exhibit a pulsation of the tumor in aneurysm and at times in fluid, but not in new growths. Oblique and lateral skiagrams are necessary to determine the location of the mass in the anterior or posterior mediastinum.

Differential Diagnosis of Mediastinal Pleurisy.—Aneurysm of the aorta can be differentiated by the pulsation of the tumor visible through the fluoroscope and the absence of septic symptoms. New growths in the mediastinum present the greatest difficulties, since there may be fever from necrotic processes and an exudate may be associated with the tumor. The antecedent history will often be as valuable as the photograph in determining the nature of the mass. Suppurative mediastinitis is almost indistinguishable from a mediastinal pleural exudate. Pericardial effusion produces a characteristic pyramidal shadow with obliteration of the cardiophrenic angles, in addition to other well-known signs, such as dyspnea and muffling of the heart sounds.

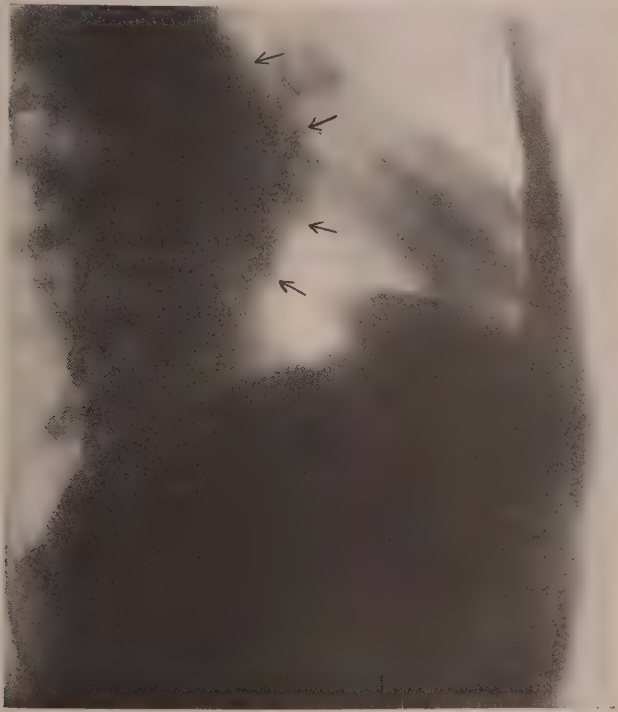

FIG. 11.—Mediastinal Abscess following Pneumonia (lateral view).

Treatment by drainage is not imperative if the effusion is serous and there is little toxemia. Empyema, however, should be always drained. The surgeon has a right to demand of the internist a preliminary localization of the abscess by exploratory puncture. Then thoracotomy is certain to be successful and the operation is simplified.

(5) *Pericardial Pleurisy*

Inflammation of the contiguous layers of the pleura and pericardium is of interest because of its frequent confusion with true pericarditis, or inflammation of the inner pericardium. The pleuro-pericardial friction sounds are generally audible during inspiration and diminish in intensity or disappear with cessation of breathing. The classical sound of pericarditis is a to and fro friction, heard during apnea and synchronous with the heart beat.

The danger of extension directly from pleura to the inner pericardium seems to be negligible. Pus pockets may form between the visceral pleura and the pericardium. The reported cases are mostly of streptococcus origin and are seldom recognized during life.

(6) *Pleurisy with Multiple Serositis*

This is a rather rare complex of pathological conditions in which pleurisy pericarditis, peritonitis and perihepatitis are combined. The origin of the disease is obscure, but tuberculosis and syphilis are supposed to be the most common infective agents.

The infection most frequently begins in the peritoneum and later involves the capsule of the liver, the pleura, especially on the right side, and the pericardium. A serofibrinous effusion is the rule in all the serous cavities, followed by slow absorption and great thickening of the membranes. The abdominal viscera are glued together in a fibrous mass, and the pleural and pericardial sacs may become obliterated. A singular fact is that the viscera themselves are not involved, the infection being confined to the membranes. The course of the disease is slow. Treatment of the pleurisy is symptomatic, including aspiration for the relief of pressure.

(7) *Pleuropneumonia Associated with Subcutaneous Emphysema*

Reference has already been made to the occasional occurrence of subcutaneous emphysema following thoracentesis from puncture of the visceral pleura. Spontaneous emphysema under the skin has been a rare complication of pneumonia in the past. But during the recent influenza epidemic many cases were reported from military hospitals as coming on during the acute stage of bronchopneumonia. The peculiar crepitation and edema appears first in the subcutaneous tissues of the neck and upper chest, spreading to the face and arms and often to the abdomen. Pneumothorax is exceptional.

The sputum exhibits a variety of organisms. Berkeley and Coffen[36] found in a series of 21 cases, type IV pneumococci in 9, non-hemolytic streptococci in 8, influenza bacilli in 3, and tubercle bacilli in 1 case. They describe two routes by which the air escapes from the lung into the subcutaneous tissues. (1) The intrapleural route, by which the air passes through both visceral and parietal pleurae. Pneumothorax may occur, but if adhesions are present the air may not enter the pleural cavity. (2) The extrapleural route. At autopsy a rupture of an air sac in the peripleural borders of the lung may be found with excavations of air covered by tense pleural membrane. From this point "air streaks" follow the blood vessels to the hilus into the posterior mediastinum. Thence the air dissects its way into the superior mediastinum and enters the subcutaneous tissues in the neck.

The prognosis is naturally more grave as a result of this complication, but many cases recover. No special treatment is indicated.

II. Non-inflammatory Fluids in the Pleural Cavity

Hydrothorax

Hydrothorax is a clear, serous non-inflammatory effusion in the pleural cavity. The fluid is a transudate in distinction from the exudate of pleurisy. Hydrothorax is usually a feature of a general dropsy and consequently is most often associated with cardiac and renal disease. The transudate from a decompensated heart may be unilateral, and in that event has a decided predilection for the right side of the chest, or bilateral with a greater amount of fluid in the right pleural cavity. The relative frequency of right sided effusions has been attributed to compression by the dilated heart upon the azygos major vein which drains the right costal pleura. (Stengel[37].) Another explanation advanced by Fetterolf and Landis[38] is that the fluid escapes not from the parietal but from the visceral pleura, and is caused by dilated portions of the heart pressing on and partly occluding the pulmonary veins. Hydrothorax from renal disease is generally bilateral. A bilateral transudate may complicate pernicious anemia, leukemia or cachetic states. Other causes of hydrothorax, usually unilateral, are thoracic tumors which obstruct the circulation, such as carcinoma or enlarged glands.

Symptoms.—Since hydrothorax is not a disease entity the constitutional symptoms are those associated with the basal process. The onset is usually insidious and is overlooked unless routine examinations of the chest are made in cardiac and renal diseases. Pain is absent and there is no fever attributable to the effusion. The tendency of hydrothorax is to produce dyspnea, but this may have preexisted as a result of the kidney or heart affection. Increasing dyspnea, at any rate, should impel one to frequently examine the thorax for fluid.

There is no friction sound, and the fluid being unrestricted by adhesions, is more moveable than that of pleural exudate. In other respects the findings are similar to those described in pleurisy with effusion.

Edema of the lungs may cause enough dullness at the base to be a source of confusion. The X-ray is useful in certain cases in demonstrating fluid. Thoracentesis is, however, the simplest method of clinching the diagnosis. The fluid is clear, of low specific gravity (1.004 to 1.015) and contains few cells. Cultures are sterile.

Successful control of the general dropsy by cardiac stimulants, diuretics and purgation will bring about the absorption of a moderate hydrothorax. Should the accumulation be large, it is advisable to aspirate. The relief of dyspnea is often astonishing and may be the turning point in the restoration of the cardiovascular balance. A limitation of the liquid intake to 1,000 c.c. per diem is serviceable in delaying or preventing the return of the fluid.

Hemothorax

Hemothorax is an effusion of blood in the pleural cavity. Hemothorax is distinct from the inflammatory hemorrhagic exudate. The source of hemorrhage in the pleural cavity is from the rupture of a thoracic blood vessel or of an intercostal artery. The bleeding may be spontaneous or traumatic.

1. Spontaneous hemothorax in the majority of instances follows the rupture of an aortic aneurysm. The blood usually escapes into the left pleural cavity and may completely fill that side of the chest. Less frequently an abscess of the lung causes erosion and bleeding from a small thoracic artery. Rupture of varicose veins created by the presence of cancer or other tumors is the occasional starting point of hemorrhage.

2. Traumatic hemorrhage is more common than the spontaneous form, but it is of more interest to the surgeon than to the internist. All perforating wounds of the chest are likely to produce more or less bleeding in the pleural cavity because of the exposed position of the intercostal arteries. Injury to the thoracic vessels from penetration of the lung does not necessarily cause hemorrhage, provided the larger vessels are not implicated. A bullet wound may penetrate the lung without causing any serious damage. Murphy[39] states that hemothorax occurs in sixty to seventy per cent. of penetrating bullet wounds as a result of laceration of the intercostal arteries. The bleeding is often slow and continuous, and if the soldier is moved about, there is great danger of secondary hemorrhage.

Symptoms and Signs of Hemothorax.—The accumulation of blood in the pleural cavity produces dyspnea and pressure symptoms in proportion to the amount present. In addition to the mechanical disturbances there is anemia from the loss of blood, and often air hunger. After penetrating shell wounds in battle the patient is in a condition of shock, which is a consequence of concussion as well as of hemorrhage. The pulse is weak and the skin moist from profuse perspiration. Fever sets in within two or three days in the larger accumulations.

Infection is a frequent complication of traumatic hemothorax and is manifested by symptoms of progressive sepsis and irregular fever, more pronounced than in uncomplicated cases. Leucocytosis is moderate after considerable hemorrhage and usually high following pyogenic infection.

The presence of blood in large amount obliterates the intercostal depressions and immobilizes the affected side. The displacement of the heart is quite constant. Tactile fremitus is more completely lost than in serous effusions. Percussion elicits a dull or flat note over the fluid. Shifting of the dullness on changing position is often observed. The tympanitic note of pneumothorax over the fluid level may be present, signifying either the entrance of air or the formation of gas from anaerobic organisms.

The breath sounds are faint, distant or suppressed. The voice is distant or nasal (egophony). When air or gas is present succussion sounds may be obtained. When the aspirating trocar is used, the blood usually flows out readily and shows little tendency to clot. After a few days have elapsed in the traumatic cases, pus cells and various bacteria are often mixed with the blood.

The sudden development of dyspnea, air hunger, anemia and shock, without pain and without fever, is suggestive of hemorrhage. Pneumothorax is the only other thoracic condition that is capable of simulating these symptoms. Physical examination and exploratory puncture confirm the diagnosis. In the presence of a penetrating chest wound the complication of pneumothorax is always looked for and requires differentiation only from pleurisy with effusion.

Treatment of Hemothorax.—Any treatment is likely to be unavailing in hemothorax from the rupture of aneurysm. Smaller collections of blood accompanying tumors should be treated conservatively. It is well to bear in mind that the chest wall as well as the weight of the fluid offers considerable resistance to the bleeding vessels. Premature evacuation removes the compression and may encourage further hemorrhage. Massive accumulations demand the withdrawal of a part of the fluid to forestall fatal syncope. In such cases the introduction of air in moderate quantity serves to lessen the engorgement of the thoracic blood vessels.

Traumatic hemothorax should be under the care of a surgeon. The Report of the Research Laboratory American Expeditionary Force[40] on intrathoracic surgery emphasizes the following points:

1. Simple hemothorax limited in amount and without symptoms, should be treated expectantly. When signs of a rapid increase in amount or of infection develop, radical treatment is indicated. If the hemothorax is large, and particularly when dense clots are demonstrable fluoroscopically, radical treatment promises earlier and more complete recovery, with slight if any increased danger. The decision as to the treatment of moderately extensive hemothorax must depend on many factors, preference being given to conservation.

2. Hemothorax with symptoms of acute anemia and continued bleeding demands measures to obtain immediate hemostasis, the safeguarding against secondary hemorrhage, blood transfusion, and when possible, repair according to established principle.

3. Hemothorax with symptoms of respiratory and circulatory embarrassment due to pressure offers a better chance of recovery if immediate surgical care is given, including accurate hemostasis and repair of visceral injuries.

4. Through and through chest wounds from bullets or shell fragments in the absence of the above symptoms are non operative types under ordinary conditions, and always so under battle pressure. For the failing circulation of exsanguinated patients, transfusion of blood is of value. When a donor is not available normal salt or the "gum salt" solution may be employed.

Chylothorax

A milky fluid in the pleural cavity is termed chylothorax. Three types of chylothorax are distinguishable, the chylous, chyliform and pseudochylous.

1. Chylous fluid has a milky appearance, does not coagulate, does not undergo putrefaction, and contains fat globules in a state of fine division. It is often associated with chylous ascites. The condition originates from a rupture of the thoracic duct or from obstruction of the thoracic or smaller lymphatic ducts as a result of the pressure of tumors in the thorax. Other etiological factors are thrombosis of the left subclavian vein and the occlusion of the lymphatics by trichinae.

2. The chyliform effusion has an appearance much like that of the chylous type, but contains a higher percentage of fat and the globules are larger (Norris and Landis[24]). Pus and endothelial cells in the process of fatty degeneration are present in the fluid. The chyliform effusion is most often associated with new growths and tuberculosis. Clinically the chronicity of the condition is remarkable.

3. The pseudochylous type is a sero-chylous fluid, less consistent than the preceding forms. There are no fat globules to be seen under the microscope. The opacity may be due to different substances. Wallis and Schölberg[41] describe a lecithin-globulin, the removal of which renders the fluid clear. West[42] attributed the milky appearance in his case to calcium phosphate.

Treatment follows the general indications of all pleural effusions Only temporary and symptomatic relief can be expected from drainage.

III. PNEUMOTHORAX

Etiology

Air or gas may gain entrance into the pleural spaces by several routes: (1) through an opening in the thoracic wall, by way of the aspirating needle or of penetrating wounds; (2) through a break in the visceral pleura and alveoli of the lung; (3) through a fistulous communication with the alimentary tract; (4) by the formation of gas on the part of anaerobic bacteria present in the cavity.

It is apparent that an opening, which permits access of air from an infected lung or hollow viscera or from outside the chest wall through a dirty wound, is likely to admit bacteria at the same time. Consequently infective pleuritis is the usual sequel of pneumothorax, and an effusion, either serous (seropneumothorax), or purulent (pyopneumothorax), may be expected. Even the escape of air from a non infected lung or the introduction of air through a clear opening in the chest wall tends to excite a pleural exudate in certain cases. Air injected into a healthy pleural cavity rarely excites effusion. But when the pleura is inflamed, as in dry tuberculous pleurisy, air may induce a serous outpouring.

1. Pneumothorax occurring accidentally during aspiration of pleural effusions, is frequently encountered. A careful examination of the chest the day after tapping often reveals above the fluid level a circumscribed area of tympany or even succussion sounds. A slight leak in the connections of the aspirating apparatus may admit the air or when the canula is cleaned out with a stylet an opportunity is given for air to enter, especially toward the end of aspiration when there is a strong negative intrapleural pressure. The air is absorbed in a day or two and does no harm. The introduction of air for therapeutic purposes will be referred to later.

Perforating wounds of the chest frequently lead to pneumothorax. A bullet wound may go through the chest wall and lung without causing pneumothorax. But many bullet wounds and practically all penetrating shell injuries are followed by pneumothorax. In external pneumothorax the wound may be closed, or may be open allowing continuous entrance of air. The first efforts of the surgeon are to close the perforation. Infection of the cavity and pleuritic effusion are almost constantly a sequel in this group of cases.

2. Perforation of the visceral pleura and lung by a sudden rent of the visceral pleura is responsible for a large number of cases of pneumothorax. It results from the erosion and rupture of the outer surface of the lung, in tuberculosis, pulmonary abscess and gangrene, bronchiectasis and pleural empyema. Tuberculosis outranks all other diseases combined as an etiological factor. The weakening of the alveolar walls may lead to rupture during a coughing spell in chronic emphysema or in the acute emphysema of whooping cough. In all these diseases cough, by its sudden violent increase of intrapulmonary pressure, may be the exciting cause of perforation. An "open" pneumothorax permits the air to enter and escape alternately with inspiration and expiration through the perforation. A "closed" pneumothorax is one in which the perforation becomes sealed after the first escape of air. A "valvular" pneumothorax is one in which air enters the cavity during inspiration but cannot escape during expiration. Perforation is most frequently found post-mortem in the upper lobe in the space bounded by the second and fifth ribs and laterally by the axillary and mammary lines.

3. A fistulous communication with the gastrointestinal canal is occasionally a cause of hemothorax. Carcinoma of the esophagus or stomach may initiate a fistulous opening into the pleural cavity with escape of gas. A subphrenic abscess occasionally perforates the diaphragm and produces empyema, which in turn finds an outlet through the lung, thus permitting the entrance of air.

4. Gas formation from anaerobic bacteria is exceptionally seen in the putrefactive empyemas of shell wounds or in non traumatic infections.

Symptoms of Pneumothorax

In a typical case of spontaneous pneumothorax occurring in phthisis, during a coughing paroxysm, the patient complains of a sharp, stabbing pain in the chest, the evidence of a localized pleurisy. Dyspnea may be intense to the point of suffocation. The pulse is rapid, the skin is wet with profuse perspiration. The picture is that of profound shock. Death or recovery ensues, depending on whether the perforation remains open or closes as the lung retracts. The valvular perforation tends to constantly augment the pneumothorax during inspiration without allowing the escape of air during expiration. Under favorable circumstances the degree of compression becomes stationary, and little by little absorption brings gradual relief.

A similar group of cases is characterized by a slow insidious onset and the recognition of the pneumothorax is first by examination of the chest or by the X-ray. Pain may be absent in these patients and the dyspnea is not conspicuous.

Pneumothorax from wounds of the chest has a symptomatology depending upon the size of the opening and whether it can be closed. Free admission of air not only brings about collapse of the lung on the affected side, but by pressure on the mediastinum greatly embarrasses the opposite lung. Extreme dyspnea and circulatory failure may occur in the large or persistent openings.

Signs of Pneumothorax

The affected side of the chest is larger than the normal and less mobile. The expiratory excursion is slight in comparison with the exaggerated movements of the other side. Litten's shadow is absent. Displacement of the heart takes place, but the apex impulse is difficult to see or is not visible, because the air on one side and the compensatory expansion of lung on the other overlie the organ. The tactile fremitus is diminished or altogether absent. The lower edge of the liver, displaced downward, can be felt in right sided pneumothorax.

The percussion note is loud and deep toned. The sound varies according to the state of tension of the gas. When under much tension the note is high pitched like the Skodaic resonance or is even dull; when under low tension the note is tympanitic like that elicited over the intestines. As the fluid accumulates, dullness appears below and tympany above. The level of fluid is a horizontal line unlike the curved line of ordinary effusion. The level shifts as the position of the chest changes. A peculiar cracked pot resonance (Wintrich's sign) may be elicited if there is a communication between the pleural cavity and a bronchus.

As a rule the respiratory murmur is faint or absent. At times distant amphoric breathing can be heard. Râles high pitched and clear are audible over the area of the collapsed lung. One of the characteristic signs of pneumothorax is the "metallic tinkle," that is sometimes produced by coughing or deep breathing. The voice sounds may be muffled and distant or amphoric in quality. The succussion sound, first described by Hippocrates, is pathognomonic of air combined with fluid. To elicit this sign the patient is given a quick shake while the ear is applied to the chest. A splashing sound is distinctly heard and may be audible to the patient himself. The coin sound is produced by tapping a coin laid flat on the chest with another coin or piece of metal, while the clinician listens over the different areas of the chest. By careful examination this phenomenon can be observed in the great majority of cases of pneumothorax.

Diagnosis of Pneumothorax

The onset, history and physical findings are generally adequate to make the diagnosis. Distention of the stomach with gas and liquids is sometimes mistaken for a left sided pneumothorax, as it presses on the diaphragm and gives a tympanitic percussion note over the lower thorax. This condition also gives rise to the succussion splash, the metallic tinkle and rarely to the coin sound. The history of the patient and the X-ray will clear up a doubtful case. A large tuberculous cavity of the lung may present amphoric breathing, tympany and the metallic tinkle, but seldom the coin sound and never the succussion splash. With a cavity there is no bulging of the interspaces, and no displacement of the thoracic viscera.

Emphysema, by reason of a tympanitic note and faint breathing, has been confused with pneumothorax. Emphysema is generally bilateral and not associated with fluid in the chest. A pleuritic effusion may compress the lung above the fluid level so that the hyperresonant note closely simulates the tympany of pneumothorax.

Subphrenic gas arising from perforation of the stomach may closely resemble pneumothorax. The X-ray will closely define the outline of the diaphragm and show the gas below. The diaphragm, in a case under our observation, was forced three or four inches above the normal position.

Diaphragmatic hernia in which the gas filled intestine or stomach protrudes into the thorax is very difficult to distinguish from true pneumothorax. The diagnosis may be made by hearing borborygmus or more certainly by the X-ray picture.

Prognosis

The mortality of all cases of spontaneous pneumothorax is said to be about seventy per cent. There is practically no danger from partial pneumothorax resulting from accidental admission of air during thoracentesis. The outlook is favorable in the pneumothorax complicating emphysema and whooping cough. Following empyema the prognosis is not so good. Cases associated with tuberculosis, abscess and gangrene rarely recover. Pneumothorax resulting from chest injuries is always a serious menace to life. According to Duval[43] fifty per cent. of patients with lung wounds die within the first day, as a consequence of pneumothorax and hemorrhage. The mortality in gaping wounds is nearly twice as high as in closed wounds, since the pneumothorax is greater and infection more frequent.

Treatment of Pneumothorax

For the state of shock induced by the sudden rupture of the lung, a hypodermic injection of morphin is indicated. This alleviates the dyspnea and lessens the cough. Thoracentesis is not a safe procedure as it is in simple pleuritic exudates and should be employed after only mature consideration. The pressure of the intrapleural air collapses the lung and is itself the best means of closing the perforation. Aspiration of the air tends to reopen the wound and aggravate the condition. If asphyxia develops, aspiration of a small portion of the air may be necessary, although there is no certainty of giving relief.

In seropneumothorax accompanying pulmonary tuberculosis, the chances of recovery are better if there is no surgical interference. The presence of pus with air must be treated along the same lines as simple empyema, namely, free drainage by incision. The certainty of progressive sepsis in these cases outweighs the danger of expanding the wounded lung. Likewise a putrid exudate with gas allows no alternative to thoracotomy. The same principles are followed in the treatment of pneumothorax from chest injuries. It is not necessary to remove the gas unless an extensive hemothorax or empyema render free drainage imperative.

Gaping chest wounds should be closed as soon as possible. Graham and Bell have shown that asphyxia occurs when the proportion of air in the pleural cavity exceeds a certain ratio to the amount of air entering the lungs. Conditions tending to limit the entrance of air into the lung, such as pneumonia, phthisis and collapse of lung tissue, enhance the danger of admitting air freely in the pleural cavity. Hence in open chest injuries involving the lung every effort is made by the surgeon to convert the open pneumothorax into a closed pneumothorax.

Artificial Therapeutic Pneumothorax

Induced pneumothorax is a form of therapy employed to compress and to encourage healing of a tuberculous lung. It is based on the principle of rest and immobilization of the infected organ. It has long been recognized that a pleuritis exudate or a spontaneous pneumothorax may exert a favorable influence on a phthisical lung. Artificial hydrothorax has been recommended as a therapeutic measure, but has not been extensively practised. Artificial pneumothorax was first advocated by Forlanini[44] in 1822 and popularized more recently by Murphy[45] and Brauer[46]. The method used by Forlanini was a simple thoracentesis and introduction of nitrogen gas through the hollow needle. The Murphy-Brauer technique was to incise the chest wall and expose the pleura before injecting the gas, in order to avoid puncture of the lung tissue.

The prospects of cure by pneumothorax therapy depend upon bringing about compression and collapse of the diseased lung. The chief obstacle to the accomplishment of this end is the presence of adhesions. The firmer and more extensive the adhesions, the more difficult it is to introduce a large amount of gas and thereby collapse the lung. The most favorable cases are those in which the adhesions are limited to the upper lobe, allowing the air cushion to produce atelectasis and retraction of the lower lobe.

Murphy believed that early tuberculosis offers the best conditions for pneumothorax treatment because firm adhesions have not yet formed. On the other hand the incipient cases of phthisis are so amenable to treatment by the ordinary means of rest, fresh air and liberal feeding, that it is doubtful if the procedure is advisable. Advanced phthisical patients who have ceased to improve under ordinary treatment are desirable subjects for pneumothorax (Robinson and Floyd[47]). Many of these hopeless cases after gas injections show an amelioration of symptoms and may enter a quiescent stage of the disease.

Bilateral pulmonary tuberculosis was formerly considered a contraindication for pneumothorax therapy. But recent writers have obtained good results in these cases by introducing the gas in the side most advanced and active. When the lesion on one side is healed the objection to compression of the other actively diseased lung is negligible.

It is claimed that the gas compression of a tuberculous lung produces anemia of the tissues, which in time lessens the bronchial and lung secretion. At any rate the retraction of the lung is followed by a gradual diminution of the sputum. There is also evidence of reduced absorption of toxic material in the lowering of temperature and gradual cessation of night sweats.

Careful observations with the X-ray have further demonstrated a diminution in the size of cavities and the formation of fibrous tissue about them; also a thickening of the peribronchial structures, such as occur in healing. At times a small amount of pleural effusion follows the introduction of nitrogen in the cavity, but this is of no consequence. Recently there has been a revived interest in therapeutic pneumothorax and its more extensive employment is urged in incipient cases[48, 49, 50, 51].

A satisfactory apparatus is that of Robinson. The gas should be filtered, injected slowly and should not exceed 200 to 500 c. c. The X-ray is valuable in controlling the operation and observing the effect upon the lung. When absorption of the air has taken place the injection may be repeated.

IV. Neoplasms of the Pleura

New growths of the pleura are nearly always secondary to tumors in the neighboring viscera. A primary tumor may originate from the cells lining the pleura. Lipoma, sarcoma, carcinoma and endothelioma are all found in the pleura. Fibroma and lipoma are the principal benign tumors.

Of the malignant tumors, endothelioma or pleural carcinoma is the most important. The tumor may be primary, arising from the pleural lining, or in the lymphatic vessels of the pleura, or secondary to carcinoma of the breast, stomach, lungs or esophagus. According to Lord not more than fifty cases of primary endothelioma are recorded in the literature. The disease may present a simple thickening of the pleural membrane or nodules of varying size. Hemorrhagic exudate is quite constant. There is a marked tendency to the formation of metastatic growths in the supraclavicular, axillary and mediastinal glands and in the lung tissue.

Primary sarcoma of the pleura is exceedingly rare. As a rule it is a nodular tumor and excites a serous or bloody effusion. Except for its disposition to occur in the earlier decades of life, it bears a strong clinical resemblance to endothelioma. Secondary sarcoma has its origin most frequently in the glands or bones.

Symptoms and Signs of Neoplasm of the Pleura

Benign tumors seldom give rise to symptoms other than that of local pressure. Malignant growths of the pleura are characterized by pain in the chest, which is aggravated by respiratory movements. There may be a cough, but it is not always present. Dyspnea develops in proportion to the amount of fluid in the chest and to the compression of the lung and the heart. Fever is exceptional.

The physical signs are those of a pleural exudate. Examination of the fluid shows the presence of blood, which increases with each successive tapping; it may become coffee-colored. Under the microscope endothelial cells are found in abundance, with comparatively few leucocytes. The fluid reaccumulates rapidly and the patient becomes anemic and cachectic.

Diagnosis

In most instances of malignant tumors of the pleura the initial diagnosis is of a pleural effusion. When the exudate is withdrawn and found to be hemorrhagic the suspicion is aroused of tuberculosis or neoplasm. Histological section of a supraclavicular lymph gland may permit a differentiation. Absence of fever, of advanced tuberculous lesions in the lungs, and of tubercle bacilli in the sputum, furnish evidences against tuberculosis. On the other hand a history of a preceding cancer of the breast, of the gastrointestinal tract or of the prostate, may weigh in favor of a secondary neoplasm.

The X-ray usually presents a nodular mass in sarcoma in contrast to the diffuse pleural thickening in endothelioma, but the two varieties of tumors cannot always be distinguished during life.

Prognosis.—The duration of life in malignant pleural tumors varies from three to eighteen months. The end is often hastened by some intercurrent infection, such as bronchopneumonia.

Treatment.—The administration of morphin is advisable to control pain. Tapping the chest for withdrawal of fluid gives temporary relief in some cases. Occasionally, however, drainage of the fluid augments the pain while it mitigates the dyspnea. In a case of the author's the pain following the tapping was relieved by injecting 100 to 200 c.c. of sterile air after withdrawing 500 to 1,000 c.c. of fluid.

V. Echinococcus of the Pleura

Echinococcus is the most common of the animal parasites to invade the pleura. The ovum of tenia echinococcus has its habitat in the intestine of the dog and is expelled in the feces. When ingested by man through the medium of contaminated water or hands, the ovum reaches the stomach and loses its outer covering. Thereupon it penetrates the stomach wall and in the majority of cases reaches the liver. Frequently the ovum gains access to the pleura and lung, presumably by way of the diaphragm. The relative frequency of invasion of the right lower lobe suggests the likelihood of a route from liver to the pleural cavity. Once lodged in the pleural membrane or lung the ovum undergoes transformation into a cyst, on the inner wall of which daughter cysts grow and develop. Hydatids usually invade the lung, but may be confined to the pleural membrane. Eventually the cyst ruptures and the clear fluid contents containing the hooklets escape either into a bronchus, or the pleural cavity, or through an erosion fistula into the chest wall.

The early symptoms of echinococcus infection of the pleura are purely mechanical, the patient showing no evidence of toxemia. Cough and dyspnea may accompany the growth of the tumor. Hemoptysis usually occurs after rupture into a bronchus associated with expectoration of the cystic fluid and hooklets. There is little or no fever. Pain is complained of when there is pleuritic inflammation. If the cyst becomes infected and purulent the patient becomes septic; spontaneous rupture through the chest wall may take place. A sudden rupture of a cyst in the pleural cavity often proves fatal. In some cases gangrene of the lung and surrounding tissues may ensue. The pleural cavity is sometimes invaded by cysts of the liver, which rupture through the diaphragm and ultimately find an outlet through the lung and bronchi.

A tumor mass may be made out by percussion, and a localized bulging of the chest wall may be visible. Vesicular breathing is absent and voice sounds distant. After the cyst has been emptied spontaneously or by tapping, amphoric breathing and a tympanitic percussion note may be elicited. A marked eosinophilia has been observed in most cases of hydatid infection. The complement fixation test may identify the specific antibodies of echinococcus infection.

As the disease is largely confined to men living in association with dogs, such as occurs on the ranches of Australia and South America, one should inquire into the patient's previous residence. The diagnosis is rarely made before the rupture of the cyst. Then the expectoration of clear fluid containing hooklets and the signs of tumor or fluid at the right base reveal the condition. The X-ray photograph may show an annular shadow. A tumor mass in the liver and eosinophilia in the blood often furnish the clew to diagnosis.

Therapy is unsatisfactory as nearly all cases terminate fatally. Aspiration of the cyst has been followed by recovery, but since the operation is likely to rupture the cyst, it is attended by unusual danger. Thoracotomy with an attempt to remove the cyst without rupture is a more rational procedure.

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CHAPTER VI

DISEASES OF THE MEDIASTINUM

BY JAMES S. McLESTER

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GENERAL CONSIDERATIONS

The mediastinum is of interest because of the important structures it contains. This interest is increased by reason of the inaccessibility of these structures and the consequent difficulties which surround all operative attempts within this space. At the same time, it is not customary in writing of the mediastinum to consider those diseases to which all these very structures are subject, such, for instance, as aortic aneurysm or myocardial disease, since these are dealt with more appropriately elsewhere, but rather to discuss those pathological processes which involve chiefly the lymphatic tissues and the framework of the mediastinum. Such processes may originate locally, may appear as metastatic invaders, or may come by extension from surrounding structures. The patient is usually apprised of their presence by pressure effects.

Anatomically the interpleural space, known as the mediastinum, is limited anteriorly by the sternum and posteriorly by the spine. It is divided into a superior and an inferior mediastinum by the upper border of the pericardium, and this latter space in turn into an anterior, a middle and a posterior mediastinum, with the pericardium and its contained heart occupying the middle space.

Viewed from a clinical standpoint, this space is best considered as a whole, or perhaps roughly divided into anterior and posterior parts. The structures contained in the mediastinum are: the heart enclosed in the pericardium; the aorta with its great branches; the superior vena cava with its tributaries; the inferior vena cava; the pulmonary artery and veins; the thoracic duct; the vagus, cardiac, phrenic, and left recurrent laryngeal nerves; the esophagus, the trachea and bronchi; the remains of the thymus gland; and numerous lymph nodes.

The functions of the mediastinum have been defined as threefold[1]: (1) it forms a septum between the two lungs, making each more or less independent of the other as regards intrathoracic pressure; (2) it lodges certain important channels of communication; and (3) it serves as a lymphatic area which contains many nodes and toward which all lymph channels lead.

Classification.—For our present purposes the following classification of diseases of the mediastinum seems best:

I. *Tumors of the Mediastinum:*
  A. Solid Tumors.
    1. Sarcoma and Lymphosarcoma.
    2. Carcinoma.
    3. Endothelioma.
    4. Thyroid Tumors.
    5. Fibroma, Lipoma, Myoma and Chondroma.
    6. Enlarged Lymph Nodes.
  B. Cysts.
    1. Simple.
    2. Echinococcus.
    3. Dermoid.
II. *Inflammation of the Mediastinum:*
  1. Lymphadenitis.
  2. Acute Mediastinitis.
  3. Chronic Mediastinitis.
III. *Other Diseases of the Mediastinum:*
  1. Emphysema.
  2. Hemorrhage.
  3. Hernia.

SOLID TUMORS OF MEDIASTINUM

Since the symptoms and signs of a mediastinal tumor are dependent upon its size, location, and consequent pressure effects, rather than upon its nature, and since at the bedside it is frequently impossible to determine the pathological character of such a growth, the following discussion will consider all solid tumors as a whole.

Sarcoma is the most common mediastinal tumor. It may be of the spindle cell variety, though rarely a giant cell or melanotic sarcoma is encountered, or it may belong to that group of tumors of varying cell type and behavior to which the name lymphosarcoma has been given. Among these last should be included the round cell sarcoma, the lymphoma, the lymphocytoma, and such borderline tumors as the so-called lymphosarcoma of Kundrat or the leucosarcoma of Sternberg. The thymus tumor to which allusion is made below should also be grouped with the sarcomas.

The growth usually arises from the mediastinal connective tissues, the lymph nodes, or the thymus, rarely from the esophagus, the air passages, or the pericardium, or it may come as an extension from the lungs or pleura. Sarcoma of the mediastinum is seldom metastatic in origin.

In their gross structure the lymphosarcomas are more lobulated than the spindle cell variety. They tend to grow in the direction of least resistance and to envelop opposing structures rather than to push them aside; hence with lymphosarcomas we may expect fewer pressure symptoms.

Sarcoma of the mediastinum may occur at any age, and between ten and sixty its distribution is fairly even.

Endothelioma of the mediastinum is occasionally encountered. These tumors may arise in the lymph nodes of the mediastinum, or may come by extension from the pleural endothelium.

Primary Carcinoma of the mediastinum, contrary to the belief of earlier writers, is extremely rare. Hare reported 134 cases of cancer and only 98 of sarcoma in his collection of 520 cases of mediastinal disease, but Christian[2] very aptly calls attention to the fact that Hare accepted without question the reports of the earlier authors, many of whom wrote at a time when, in the light of our present knowledge, their diagnosis and terminology must have been faulty. He quotes Löhrish as being able to find but two instances of true mediastinal carcinoma reported in the years 1896 to 1901, and adds another reported in 1906. These tumors can originate in the mucous membrane of the esophagus, trachea, bronchi, thymus, or misplaced thyroid, sometimes from fetal inclusions.

Carcinoma elsewhere in the body differs from sarcoma in that the former is accompanied with relative frequency by metastasis in the mediastinum. Such secondary growths may have their origin anywhere in the body, but most often they come from the mammary gland or the lung and locate first in the lymph nodes at the hilus of the lung. Moderate enlargement of the posterior mediastinal lymph nodes discovered in the radiogram, is occasionally seen as the first intimation of an esophageal cancer.

The Thymus, which ordinarily atrophies before the age of carcinoma development, sometimes gives rise to a malignant tumor of homogeneous structure, whose nature is uncertain and which consists of certain round cells suggesting the parenchyma cells of the thymus. This tumor should properly be reckoned among the sarcomas rather than among the carcinomas.

A misplaced *Thyroid Gland*, situated in the thorax between the sternum and the trachea, or an accessory thyroid gland in this location may give rise to a tumor of sufficient size and rapidity of growth to embarrass the patient and produce pressure symptoms. Such a tumor may be a simple adenoma, or it may assume the malignant characteristics of a sarcoma or carcinoma.

Benign Tumors of the mediastinum are rare, and since they grow slowly and do not form metastases, they seldom produce symptoms. Most often they represent merely a chance find at autopsy. In this group belong the fibromas, lipomas, myomos, chondromas, and osteochondromas. An exception to this general statement is the dermoid cyst, which will be discussed later.

Enlarged Mediastinal Lymph Nodes, whether simple or tuberculous, deserve mention here because they sometimes form tumor masses of great size and produce pressure symptoms identical with those of other tumors. Inflammatory reaction in these tissues will be reserved for discussion with mediastinitis.

Pigmentation and sclerosis, as a part of the process known as anthracosis, is frequent in those who habitually breathe air laden with coal dust, and the mediastinal glands of stone cutters are said to show a similar sclerosis. The writer has been particularly impressed by the dark color of the bronchial lymph nodes of individuals who have lived long in the Birmingham, Alabama, district.

Simple hyperplasia of these nodes, even without infection, it is said, may take place as the result of any infection whose products drain into the mediastinal lymph spaces. Usually such masses, which are most often peribronchial, are insufficient in size to produce discomfort, but occasionally, as the result of a chronic or frequently recurring bronchitis in children, the nodes attain sufficient size to call forth definite pressure symptoms.

In Hodgkin's Disease and in leukemia similar enlargement of the mediastinal lymph nodes is encountered, and in each the masses may attain sufficient size to produce distressing symptoms. Both of these diseases are accompanied by glandular enlargement elsewhere, and before mediastinal pressure symptoms are experienced, hypertrophied nodes in the neck and other parts of the body usually may be felt.

Such masses of enlarged lymph nodes are heterogeneous in structure, consisting of a conglomerate mixture of lymphoid and connective tissues. As would be expected, they are irregular and nodular in outline, and frequently no definite boundary line can be seen in the radiogram between the tumor mass and the lung area.

Symptoms of Mediastinal Tumors

The symptoms of mediastinal tumors, confined as these tumors are in a definitely limited space which houses a number of vitally important structures, are dependent, whatever the nature of the tumor, upon the pressure which is exerted upon these structures. Every degree of pressure, constriction, and displacement is encountered in such tumors, and the widest variation in intensity and combination of symptoms.

Three clinical types can be roughly recognized: (1) tumors of the anterior mediastinum, which by obstruction of the venous circulation produce the most graphic physical signs; (2) those of the posterior mediastinum, which by pressure upon the esophagus, trachea, and intercostal nerves induce distressing subjective symptoms; and (3) those which extend from pleura or lung with both physical signs and symptoms in like proportions.

The onset of symptoms is most often gradual and slow. It sometimes happens that an individual harbors a mediastinal tumor for years with slight discomfort, yet in rare instances we may see him experience the fulminant development of all symptoms with a rapidly fatal ending.

Dyspnea, cough, and pain are the most frequent symptoms, while circulatory disturbances offer the most constant physical signs. The patient usually complains first of shortness of breath on exertion, of cough, or perhaps of both. He tells of a gradually increasing dyspnea, which at first may be paroxysmal in character, with long periods of complete relief. This may be the only symptom for months, and it must be borne in mind always that respiratory distress, which cannot be explained by disease of the heart or lungs, should suggest mediastinal tumor. Gradually the dyspnea becomes more oppressive and less dependent upon exertion or emotion as the tumor with its consequent pressure increases in size. The continuous distress and the inability to sleep in a recumbent posture leads to exhaustion, and finally only too frequently the dyspnea ends in suffocation.

Cough is a frequent symptom and is often paroxysmal in character. It may be wheezy and perhaps accompanied by stridor. A peculiarly characteristic brassy cough accompanies hypertrophy of the tracheobronchial and peribronchial lymph nodes, particularly in children.

The sputum is variable, being usually the mucous expectoration of bronchial irritation. At times it is bloody, or as evidence of a secondary infection of the air passages, it may be purulent. Its bloody character, with the fever which sometimes accompanies mediastinal tumors, has led to a mistaken diagnosis of pulmonary tuberculosis.

At first the patient may complain of a sense of constriction or oppression in the chest. Later this becomes a real pain, which is usually substernal and varies greatly in intensity and constancy. Though present in the later stages with great frequency, at times pain may be absent throughout the entire course of the disease. Dysphagia or esophageal pain is an occasional complaint, especially when the pressure of the tumor is exerted chiefly in the posterior mediastinum.

Vagus irritation may lead to asthma-like attacks or other respiratory disturbances, to cough, to spasm of the glottis, to bradycardia, or if the nerve is paralyzed, to tachycardia. Paralysis of the recurrent laryngeal nerve occurs occasionally, though less often here than in aneurysm. Even in the absence of hoarseness or other laryngeal symptoms, vocal cord paralysis should be sought for with the laryngoscope. Irritation or paralysis of the vagus from mediastinal pressure is said also to lead to such abdominal symptoms as nausea and those of gastric hyperacidity as well as to intestinal disorders. Pressure upon the sympathetic nerves may produce pupillary dilatation, exophthalmos, or one-sided hyperidrosis.

Involvement of the phrenic nerve sometimes leads to unilateral paralysis of the diaphragm, but in the same connection, it must be borne in mind that a very similar phenomenon may be produced by occlusion of a bronchus. Irritation of the peripheral nerves, particularly the rami communicantes, may produce pain at a point distant from the source of the pressure. Such a pain has been experienced in the ulnar nerve. The writer recalls a patient in whom for a long period the only symptom of a malignant mediastinal tumor was a most distressing intercostal pain.

Cachexia and fever are occasionally seen, more often in tumors of the posterior mediastinum. Pressure upon the thoracic duct is said to produce sudden wasting; occasionally chylous ascites has this origin. Headache, dizziness, and disturbances in vision are occasional symptoms.

The most marked symptoms as well as the most graphic signs are produced by pressure upon the inferior vena cava, the result of which will be discussed below. The aorta, because of the stronger arterial wall, is seldom constricted, although a pressure necrosis of this vessel with fatal hemorrhage has occurred.

Physical Signs of Mediastinal Tumor

A local bulging of the chest is frequently seen, or perhaps a fullness of the intercostal spaces, and so important is this that the slightest asymmetry should always receive attention. Localized edema and injected veins over the tumor area are sometimes observed. Sarcoma of the anterior mediastinum tends to grow forward, pushing in front of it the sternum and ribs, rarely eroding them. Enlarged lymph nodes in the neck are frequent, and occasionally the tumor mass may be felt above the suprasternal notch. Deviation of the trachea, especially in intrathoracic tumors of the thyroid gland, may indicate mediastinal pressure. Localized pulsation of the chest wall, not expansile in character, is frequently felt.

Dullness or flatness on percussion over the tumor, or perhaps merely an extension of the normal cardiac area of impaired resonance is often noted. Posteriorly under normal conditions the percussion note, which is dull over the last cervical vertebra, gradually becomes more resonant from the first to the fifth dorsal vertebra and is clear but not tympanitic from the sixth to the ninth dorsal vertebra. Tumors of the mediastinum are said to modify this clear note. Diminished or absent tactile fremitus and absence of the respiratory murmur may be noted over those areas where atelectasis of the lung has followed pressure upon a large bronchus, yet occasionally the respiratory sounds are well transmitted through such a lung. Pleural effusion is present very often and may be so extensive as to obscure the tumor.

Signs of venous obstruction do not ordinarily appear until the superior vena cava has been constricted to about three-fifths its original diameter[3]. These signs are dilation of the veins, cyanosis, and edema. At a certain stage they may be striking, later to disappear as the collateral circulation becomes well established.

Usually the veins in the neck are the first to dilate, standing out as prominent cords. Others over the neck and chest then become involved, until finally an elaborate network of prominent, outstanding, anastamosing veins has appeared to take up the collateral circulation. In typical instances the venous dilatation is general over the upper half of the body, or depending upon the location of the pressure within the chest, it may be localized. Cases of one-sided dilatation and edema have been reported. The course and distribution of these veins is more particularly described in the discussion of chronic mediastinitis. Accompanying, sometimes preceding, these startling vascular changes is a striking subcutaneous edema, first of the neck and then of the arms and chest. Rarely it may be more definitely localized.

Cyanosis develops simultaneously with the vascular changes or may appear independently. A blueness of the lips and a generally increasing duskiness of the face is often an early objective sign. This may of course be produced merely by respiratory distress before marked obstruction of the veins has occurred.

Polycythemia of moderate grade is a concomitant of the venous obstruction. The number of erythrocytes and the percentage of hemoglobin are usually high, and especially so during the paroxysms of increased dyspnea and cyanosis, when values as high as nine million and one hundred and forty-four per cent. respectively have been reported. A difference in the counts made from the ear and from the toe is sometimes noted in such patients. Dilatation of the retinal veins and edema of the optic disk is a frequent result of such circulatory disturbances.

Radiology gives valuable help in the recognition and identification of these tumors and permits a view of mediastinal masses before symptoms or pressure signs appear. Every person with a malignant tumor, wherever located, might well be given a radiologic examination of the mediastinum before operation to discover any possible mediastinal metastasis whose presence would influence operative treatment. Whenever possible, both radioscopy and radiography should be used. If one must choose, the former gives, perhaps, more valuable information, since pulsation and movement can be observed, yet the latter brings out more closely the finer details of structure and permits more precise study.

The mediastinum should be viewed from every direction, anteroposteriorly, laterally, and obliquely. The right anterior oblique direction permits a good view of the clear space between the heart and the spine. The left posterior oblique direction gives a less distinct view of the same area. Stereoscopy is useful in giving better orientation, and resort to teleroentgenography may be had as a method of recording the progress of a growth.

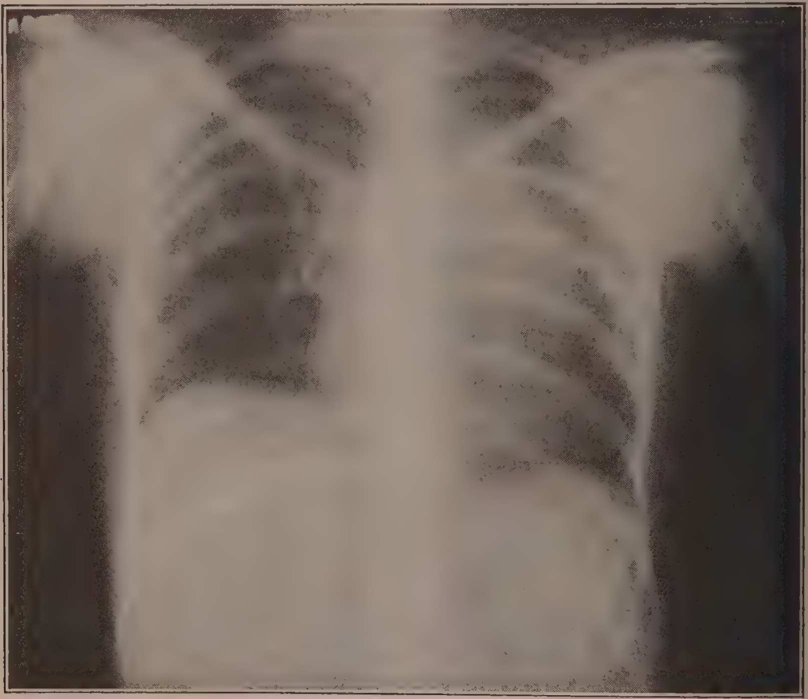

Fig. 1.—(*Case 1*) Large lymphosarcoma of mediastinum which bulged above the clavicle exteriorly, June 4, 1913. (*Courtesy of Doctor C. F. Burnham.*)

Differential Diagnosis

It is relatively easy to determine the presence of a mass in the mediastinum, and by its pressure symptoms we can usually tell something of its size and location, but the nature of the mass is only too often a matter of conjecture.

To distinguish between aortic aneurysm and a growth of the mediastinum is not always as easy as a statement of the differential signs would indicate. The presence in the former of an expansile pulsation is the classical differential sign, but it must be borne in mind that solid tumors frequently transmit a pulsation which may be deceptive in character, and that instances have been reported where an aortic aneurysm, because of a thick wall of fibrin within its sac, failed to show the typical pulsation.

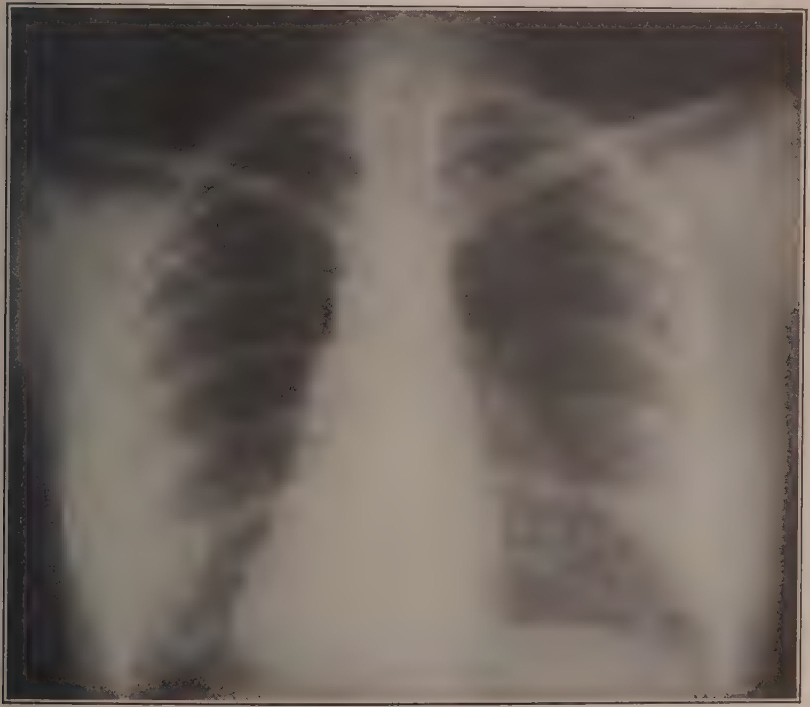

FIG. 2.—(*Case 1*) Tumor, April, 1917, practically cleared up under radium therapy. (*Courtesy of Doctor C. F. Burnham.*)

Aneurysms, best seen in the left posterior oblique position, are sharply outlined, but unfortunately malignant tumors as a rule show the same sharp detail. If beside the shadow of a mass the arch of the aorta can be recognized in normal position, this speaks against aneurysm, although the converse is not true, since a large tumor can greatly displace a normal aorta.

Certain general facts are of value in the differential diagnosis of tumors of the mediastinum. Sarcoma, which is by far the most frequent, is usually seen in the anterior mediastinum, while of the tumors of the posterior mediastinum, particularly in children, tuberculous adenitis is to be considered. The character of the sputum will sometimes disclose a dermoid cyst. The Wassermann reaction may reveal the nature of gummatous growths and is also one link in the evidence for aneurysm.

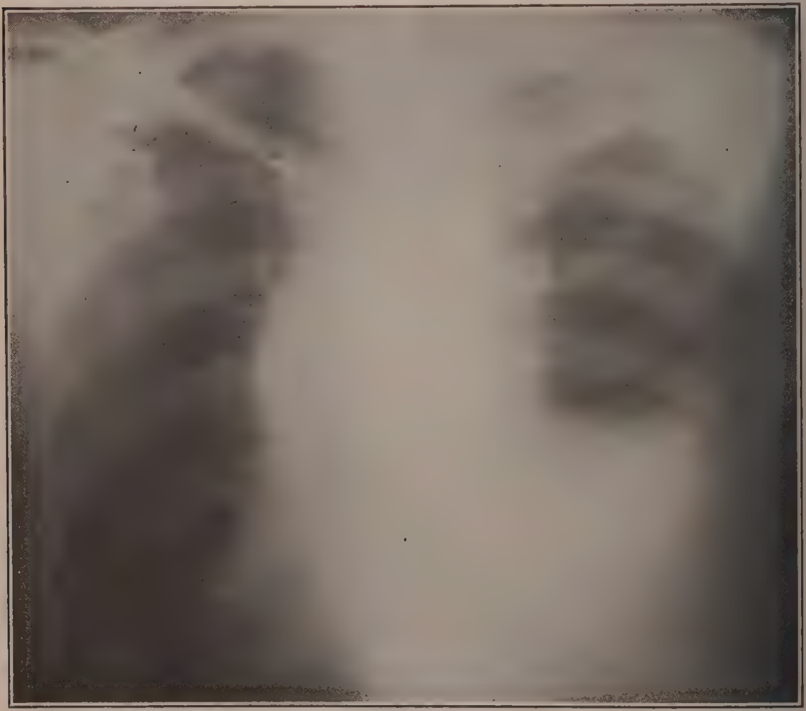

FIG. 3 —(*Case 2*) Deep seated mediastinal tumor which caused difficulty in deglutition, November 27, 1914. (*Courtesy of Doctor C. F. Burnham.*)

In distinguishing between a true mediastinal tumor and those of the lung, it is a general rule with many exceptions, that the former show sharp outlines in the radiogram while the latter reach out into the lung with irregular faint shadows.

A thorough clinical study of the patient from every standpoint is essential, for it often happens that findings outside the mediastinum will clear the diagnosis, such for instance as a malignant tumor elsewhere, the blood changes of leukemia, or evidence of Hodgkin's disease, or generalized tuberculosis.

Prognosis

Regarding prognosis, the malignancy of a mediastinal tumor depends not so much upon its pathologic structure as upon its location and the rapidity of development. Depending upon these factors, it may run a rapidly fatal course within a few months, may continue for two, three, or four years, or may pursue a relatively unobtrusive course for many years.

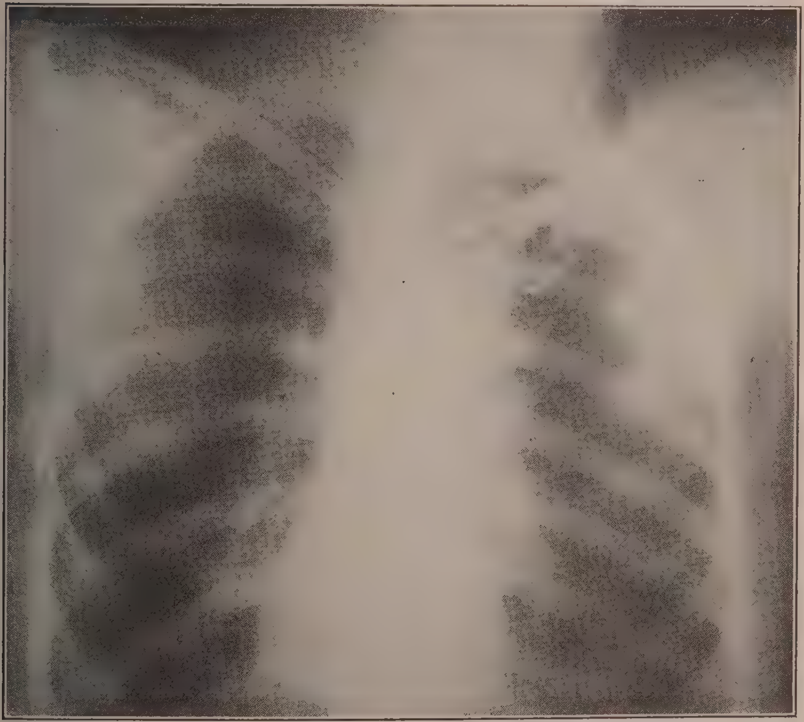

FIG. 4.—(*Case 2*) Almost complete disappearance of tumor November 8, 1915, as a result of about six months radium treatment; apparently complete recovery of patient. (*Courtesy of Doctor C. F. Burnham.*)

Treatment

Concerning treatment, malignant tumors are best treated with radium, and when this is not available, X-rays should be tried. Burnham[4] has recently reported some excellent results (see Figs. 1, 2, 3, and 4) from the use of radium in which he states that at least one gram of radium is necessary and that lead filters should be used to protect the skin. Von Bergmann advises also the energetic use of arsenic, though with what reason it is difficult to see.

Temporary amelioration of symptoms has been achieved by the surgical device of splitting the sternum and thus relieving intrathoracic pressure. Enlarged glands of the posterior mediastinum, which are producing pressure symptoms, can sometimes be satisfactorily reached by surgical measures through the back. Gummata are amenable to energetic antiluetic treatment.

Cysts of Mediastinum

Cysts of the mediastinum may be simple, echinococcus, or dermoid, and among the last named we include the teratomas.

Simple Cysts of the mediastinum, which are small and usually lined by a single layer of ciliated epithelium, are rare. Most of those reported have been in the neighborhood of the tracheal bifurcation. *Echinococcus Cysts* are also rare and grow slowly, producing symptoms only when they have reached great size.

Dermoid Cysts and *Teratomas* of the mediastinum also are uncommon. Christian[5] in 1901 collected forty cases, and in 1905 Morris[6] in an excellent summary of the literature of that time brought the total number to fifty-seven. Hertzler[7] in 1916 brings the number to seventy-three, since which time I have been able to find two additional cases[8, 9], thus giving a total to date of seventy-five.

These growths vary in complexity from the simple cyst lined by squamous epithelium, to the most complex cystic tumors, such as the one recently described by Lindstedt[8] as an "adeno-chondro-myxocarcino-sarcoma". Christian[10] classifies these cysts as: (1) dermoid cysts, of simple structure and ectodermal origin; (2) teratomas of great complexity with rudimentary organs, derived from all three germ layers; and (3) tumors of either of the foregoing classes which are malignant in some part of their structure and form metastases. For the present purposes of clinical discussion it is best to consider all three classes as one.

These cysts represent fetal inclusions, being formed in the closure of the fetal clefts or by infolding of the embryonic glandular structures. Sex has no bearing on their frequency. Although they may appear at any age, they are most often seen in the third decade.

Dermoid cysts may be found anywhere in the mediastinum, but their most frequent location is in the anterior part of the upper mediastinum. They grow variously in every direction, pushing the chest wall forward, extending above the clavicle into the neck, or reaching laterally into the area ordinarily occupied by the lungs, and not infrequently they press is usually moderate in degree, dry with but slight effusion, and more or less latent, probably being rather incidental than a direct sequel of the primary disease, often indeed only a "trouvaille de necropsie." In *malaria* I am told that it occurs only as a coincidence, and very rarely. In *diphtheria* Dr. Figdor has described a case of pericarditis with effusion in a child aged three with necropsy; in the discussion which followed, Dr. J. D. Rolleston said that the complication was very rare in diphtheria, so much so that he had never seen a case in life nor at necropsy, though in these cases the pericardium may be covered with petechiae. In some of these incidental cases in eruptive fevers, as after scarlet fever, a pericarditis may be due to a latent rheumatic infection. In *influenza* I should say that pericarditis, save as propagated from an empyema, an event only too common in the last epidemic, must be very rare; though Dr. Morton, in a recent thesis for M.B. at Cambridge, gave it as three per cent. in 170 cases; cases secondary to empyema were excluded. A latent pericarditis is said to be no very infrequent discovery in the necropsies of *cerebrospinal fever* and it is recorded as a rare event in *actinomycosis*. In *scurvy*, at any rate in some epidemics, pericarditis with sanguinolent effusion is said to have been somewhat frequent. In *syphilis* a primary pericarditis is very rare save as a more or less accidental part of a gummatous process, itself of giant cells with chains of lymphocytes and plasma cells passing into the fibrous tissue with partial adhesions, extending from other parts, as from the heart. It is almost always latent until revealed at a necropsy. Many form part of a congenital infection. Pericarditis arising incidentally in the later course of *morbid growths* needs but a passing word; these again are for the greater part post-mortem discoveries. Of such a kind is the mostly dry pericarditis which in certain rare cases is associated with an infarct of the heart's substance.

Leaving these occasional events, which are rather scientific curiosities than matters of practical importance, we may now turn to the two kinds of pericarditis that come next in frequency and gravity to the rheumatic; namely, the tuberculous and that arising in renal disease.

Tuberculous pericarditis comes next in frequency to the rheumatic, or so it is said, but I surmise that many cases of uremic pericarditis, overlooked or observed only in the post-mortem room, escape clinical record. However this may be, tuberculous pericarditis is not in my experience of very frequent occurrence as an outstanding clinical event. It may appear in one of three forms: as partaking in a general miliary outbreak, diffused over all or most of the serous surfaces and elsewhere, or as a dry and insidious process leading to symphysis, or, thirdly, to effusion often very profuse. Some of the largest serous effusions recorded in pericarditis have been of tuberculous origin. The pericardium may appear during life to be the only seat of tubercle, but tuberculous pericarditis primary and sole must be very rare. It is remarkable that it very seldom arises in the course of ordinary phthisis (Osler). Most commonly it is propagated to the pericardium from the far more common tuberculous pleurisy or from bronchial or mediastinal glands thus affected or from one or both. The pathology of it will be considered later.

The pericarditis of *renal disease* is, I think, more frequent than is generally supposed, but the larger numbers of my recollection may be fortuitous. It is usually estimated as about six to eight per cent. (Sibson, Roberts) of all cases of pericarditis; I should guess it at ten per cent. It is less frequent than the corresponding pleurisy, but is usually latent and so is often overlooked. It is to be distinguished from the hydropericardium of renal dropsy. If on the one hand it is often latent, on the other its friction, when found, is often loud and persistent. Time after time I have found it in patients going their way unaware of any serious ailment, and without localizing symptoms. I may say a brother justice, not feeling very well, walked home with me after a long sitting at Quarter Sessions; on undressing him I found a local pericardial rub; moreover, his urine was albuminous and his heart big and thick. He was very angry with me for looking gravely upon his condition, but in a few weeks he died of uremia. I had a similar experience in the case of a tradesman, at the time of my first visit engaged as usual in his office. Thus it takes a characteristic course and is of bad omen, but whether due to a toxic or microbic cause is uncertain; probably it arises from a microbic infection made easy by failing resistance. Yet it is often unaccompanied by pyrexia and is indisposed to pus formation. In the younger patients it occurs rather with parenchymatous nephritis; in the older with primary contracted kidney.

Diabetes and *gout* have been recorded as causes of pericarditis. If there is such a thing as a rub on a dry but not inflamed pericardium, diabetes might set it up; "gouty" pericarditis is probably due to renal default. Of the remoter and incidental causes, such as privation, chill, and the like, there is nothing of specific interest to be said.

Pathology of Pericarditis

The disposition of the pathological changes depends in some cases on the hematogenic origin of the inflammation and in others on its origin by extension from a neighboring lesion, as from lung, pleura, peribronchial or mediastinal glands, endocarditis, aneurysm, or ulceration of a contiguous viscus. A large proportion of the cases of pericarditis, perhaps half of them, are by such an extension. From endocarditis the extension is to the reflexion of the sac upon the roots of the great vessels, a very important clinical feature, as we will see. Extension from a pleurisy of course attacks first the outer pericardium, and if the necropsy be made at this transient stage, the inner face of this part, if rosy, may yet be smooth, and the effusion without fibrinous flakes—the so-called *pericarditis serosa*.

The pathological anatomy of pericarditis differs but little from that of inflammation of other serous membranes; and this is hardly the place to enter at length into the general characters of these inflammations. In acute pericarditis the inflammation usually arises in patches about the base of the visceral membrane where the endothelium is attacked by the microbe or its toxins, this part and the middle area being usually the first seats of it, and not by contiguity. The parietal membrane suffers chiefly on its inner face, but, as we shall see, the inflammation may penetrate outwards and set up farther an external pericarditis. On the other hand, these patches may be transient; the process may subside and end in partial adhesions or possibly in the milk-white patches so commonly seen by the anatomist on the heart's surface, especially on the anterior surface of the right ventricle. Probably in all cases the congestion of the parts affected advances more or less, the surface of the membrane loses its sheen and becomes velvety and thickened, a pink blush appears, the endothelium swells, wets, and strips off, and effusion escapes, at first in the form of tiny drops; a network of new and enlarged vessels then appears from which come transudation and diapedesis and, from minute ruptures, punctiform hemorrhages. The effusion now becomes more abundant, false extra-vascular membranes form on the surface, and fibrinous flakes float away into the serum. The fibrinous layers on the surface can be still scraped off as semi-transparent, yellowish gray, gelatinous strips which thicken by addition. These layers and the connective tissue are full of white and red corpuscles and probably of microbes. A conspicuous result of the chafing of the two surfaces of the sac is seen, especially on the right ventricle, a rubbing of the glutinous deposit into ripples or ridges and fur—*cor villosum*—a state which has been compared to that seen when two buttered plates are apposed and separated. As with plates so with the pericardium, this "*cor villosum* or *hirsutum*" is an artifact of the operator. Upon the left ventricle the lymph appears as a network or in little clumps. In the majority of cases the effusion abides as a serofibrinous liquid, but it may be stained with hemorrhage, or may become purulent. A serofibrinous effusion may amount ordinarily to 90 c.c. or 120 c.c., but in some cases may reach 250 c.c. to 500 c.c. Cases are recorded of one to two liters, many of them slow tuberculous cases. On the other hand, the effusion may be so little that the pericarditis is called "dry." The peril of the larger effusions is that the auricles become compressed so that the ventricles do not receive their due charge of blood; and under the same pressure the lungs—especially the left—may collapse. A purulent exudation may lead to ulceration and perforation towards the surface of the body or towards other neighboring parts with the formation of a sinus; but, unless by the prevention of surgical relief, the patient very rarely lives long enough for such an issue to come about. I have no recollection of any such case. Bloody effusions arise from rupture of tender new vessels in the pericardium and the false membranes. It may be unimportant in degree, but usually appears in tuberculous cases, in some senile cases, or alcoholics, or in such cachectic conditions as scurvy, cancer, malignant infections, and the like. Chylopericardium is said to have occurred, but if so, is a mere curiosity.

Fortunately in the majority of cases, even of active rheumatic fever, the exudations, after reaching a certain tolerable extent, begin to recede, and absorption of the products sets in. In rheumatic pericarditis, therefore, operative evacuation is rarely required; after the effusion has attained a certain bulk, whether by increase of pressure closing blood vessels and lymphatics or otherwise, the process is arrested and the false membranes undergo granular and fatty degeneration, so that the only remaining peril is the remote one of hampering adhesions or bands on the pericardial surfaces. It is said that *restitutio ad integrum* in every practical sense often takes place. The white patches already mentioned may be such remnants or may be due, especially in old persons, simply to chafing—"pericardial corns." They consist of scar-like tissue, the fibers of which penetrate a short way into the uppermost layers of the subjacent part of the ventricle. These patches, which now and then become calcareous, did not escape the observation of the ancient anatomists. Sometimes they are so extensive as to look like a sugar coating over the hearts. On the other hand, the effusion may be purulent, when the fluid becomes turbid with granular fibrin, and the surfaces put on an appearance like ulceration. Or again, a chronic inflammation may propagate itself to the mediastinum; usually in simple inflammations the effusions are smaller in amount. In tuberculous cases granular deposits may be seen on the membranes, or caseous inclusions may be found in pockets between the partially agglutinated coats (cloisonné). Cancer and other propagated lesions may determine inflammatory effusions or, otherwise and more commonly, these may be more or less of a dropsical kind.

This is hardly the place to enter upon the microscopy of the morbid histology which differs little from the same processes in other serous surfaces. The false membranes consist of a fine fibrinous reticulum in the meshes of which are seen endothelial cells, leucocytes, and deeper small embryonal cells; into the bands small vessels penetrate. The deposit in the limpid, colorless, or greenish fluid consists of a few leucocytes and some red cells; these become of course much more abundant in the sanguinolent exudations.

A far more important point is the condition of the myocardium. A myocarditis may be propagated directly from a visceral pericarditis, or may own an independent origin from the primary infection; or again, and this perhaps may be the most frequent condition, may derive from both sources. The morbid anatomy of myocarditis is described elsewhere, but the critical importance of this cooperating factor of evil will be considered immediately. Not only is the state of the myocardium of instant clinical importance, but the morbid anatomist knows that afterwards on recovery a more or less chronic sclerous or callous myocarditis or fibrosis may be established.

Symptoms and Signs of Acute Pericarditis

In this chapter we are not concerned with those of the various general infections from which pericarditis may arise, but only with those of the part affected. In the first place we must remember that of symptoms there may be none, that there may be neither symptom nor sign; the malady may be insidious and latent. In all cases where pericarditis is possible we must be on the watch. The attitude of the patient may arouse suspicion; sitting a little forward, leaning to the left side and complaining usually of a dull and wearisome ache rather than an acute pain in the side. In young patients, however, pain is more manifest than in older persons. In Bright's disease there is often, usually perhaps, no pain whatever, loud as the friction may be. In other cases the distress varies from this slight discomfort to a severer pain aggravated by movement, deep inspiration or cough, or to a piercing stab. It may be seated in the epigastrium, or towards the neck and left shoulder, or under the shoulder blade, or between the shoulders, when the corresponding vertebral spine may be tender to pressure. A stitch in the side would suggest a coincident pleurisy. The pericardium is well furnished with nerve end-organs. Finally, the pain may be retrosternal, as we shall note particularly in the anginiform or actually anginose attacks which occur in a few cases. Beside the anginiform pain there are two other pains perhaps not less distressing; namely, by involvement of the phrenic nerve, or by implication of the diaphragm. This last accident, whether in pleurisy or pericarditis, may set up an agony to all appearance almost mortal. If the phrenic be engaged, two tender points may be observed: the one between the two insertions of the sternomastoid muscle, the other at the xiphoid or in the angle between this bone and the last costo-cartilage on one or both sides. Not infrequently there is pain on swallowing. How such an implication of the phrenic, or of the diaphragm itself, in a pericardial or other inflammation may give rise to terrible symptoms, I recall in the case of a young lady in whom a diaphragmatic pleurisy threw the household, and indeed her physician, into consternation. For a day or two, till the inflammation crept upwards, there were little or no physical signs; still the negative points, such as the regular pulse, clear complexion, and so forth, together with arrested diaphragmatic action, will usually indicate the true diagnosis. It is said that Mirabeau was thus attacked, and in the spasms of pain cried for death. In pericarditis such an extension in the presence perhaps of serious cardiac disorder may present more difficulties, may perhaps suggest pulmonary embolism and the like, but if the physician be forewarned he will be better able to disentangle the coil. The short catching breath, seat of the pain, jactitation, and perhaps hiccough are points against angina pectoris, as in such states the dysphagia, already mentioned, may be so distressing the patient may not dare to drink. These symptoms have received the repulsive name of the hydrophobic group. In the course of a pyrexia due to other causes the intercurrence of a pericarditis may make little difference; or a sharper ascent may be noted.

Marked dyspnea is often absent during the first few days, though distension of the alae nasi will not escape notice; and the palpitation of the heart seldom disturbs the patient. But here we must turn for a moment to the effect of an effusion upon the cardio-respiratory machine. If a fluid in the pericardium be connected with a manometer the ordinary diastolic pressure, which we know is reenforced by the vagus, stands at about 19 cm. H_2O. If, however, the fluid pressure be increased, as demonstrated by the experiments of Cohnheim, and of Starling, beyond a certain limit, blood is then hindered on entering the heart, the venous pressures rise as the arterial fall, and the pulmonary second sound begins to clang. This disturbance of balance begins when about 20 c.c. of fluid have been injected; then the vagus reenforcement takes place until some 10 c.c. more have been poured in; the auricles begin to collapse, the ventricles are not supplied, and the reversal of blood pressures takes place. But in respect of surgical operation it is to be noted in these experiments that, if at this point the pressure of the injection be reduced, the heart's action is quickly restored. The pulse and respiration then betray the presence of pericardial effusion when it increases beyond a certain limit; up to this point there may be no dyspnea. Some paroxysmal dyspnea may appear before the compression, and not infrequently is accompanied by a dry expiratory cough like that of whooping cough, sometimes even to vomiting; or in some cases a toxemic dyspnea may appear. But as compression begins to tell, the pulse, always on the rapid side (120–130) and apt to exceed the respiratory ratio, becomes small, weak, and irregular, even syncopic; however, in this condition we have to remember that the myocardium may be affected, or the irritation may be due to implication of the phrenic or the diaphragm. In the case of high venous pressures some cyanosis would become apparent.

Usually in rheumatic pericarditis resorption begins before this stage is reached. The behavior of the jugular veins is not very significant; it is irregular and often equivocal; it may be normal even in effusion or synechia. We cannot rely either on systolic emptying of these veins, nor as Skoda observed, on their sudden collapse in diastole due to the drop of the diaphragm and elongation of the veins after the pull of the systole; but if the jugular pulse be very small and hard to pick up, or on the other hand is persistently distended, as it may be in compression of the auricle or vena cava, we should note it for what it may be worth, that is, for nothing very characteristic. In inspiratory filling of the jugulars, together with the pulsus paradoxus, we have a useful sign, suggestive of throttling of the vena cava by effusion or a drag on it by synechia, or of other cause. So the face may turn blue in inspiration. A jugular pulse would of course indicate an open tricuspid orifice.

The aorta may be compressed in the same way, and thus we come to the well-known pulsus paradoxus, first described by Griesinger in 1854, and not quite happily so named by Kussmaul twenty years later, who, moreover, wrongly attributed it to myocardial failure. But it is not a paradox; the phenomenon is but an exaggération of the normal pulse wave. A few weeks ago a bright, healthy, and very active little girl was brought to me for heart disease; the poor child had been forbidden to play games or even to run because her pulse was "so irregular." On analysis it was quite regular after its fashion—which was that the respiratory wave was enormously exaggerated. She was soon dismissed and under some supervision was sent to play and run as she pleased. This exaggeration, in its degree not uncommon in children, in pericardial disease may become still more extreme, so that in the inspiratory period the pulse vanishes. Effusion, mediastinal adhesions, any drag on the aorta or the subclavians, laryngeal stenosis, a large pleural effusion, or even the experiment of Müller, which anyone may observe for himself, will produce it. The conditions are inspiration, negative pressure in the thorax, and some traction on internal surfaces, such as the intra-thoracic vessels, diaphragm, or even in some degree the chest wall. Inspiration fills the jugular veins, the veins on the surface empty, and the arterial wave falls. In pericardial effusion it may for a minute or two be unilateral, as in a case I saw with Dr. Humphry. The case was an obvious one of hemorrhage into the pericardium from a ruptured coronary artery; Dr. Humphry was feeling the radial pulse on the right side, my finger was on the left; the "paradox" appeared on the left side a minute or two before it appeared on the right. The patient was lying on her back in bed. Any cause of pressure on one subclavian would of course set up a unilateral pulsus paradoxus. If the effusion be enough to compress the ascending aorta, the subclavian arteries may beat excessively and the left pupil may be dilated. In large effusion the radial pulses may be unequal. Ordinarily the pulse is quickened, and as compression by effusion increases and overcomes vagus and other resistance, or again as myocarditis may increase or invade the conducting tracts it loses volume, pressure, and regularity. It is said that the pulses may alternate; if so, myocarditis or degeneration would seem to be the certain inference. Venous stasis, on the other hand, would suggest compression of the auricles, but I have often seen what I have called the peach-like complexion in mere myocarditis without effusion.

It is convenient here to point out, as a symptom of pericarditis, arrest of abdominal breathing as pointed out by Hilton, Barlow, and others. Such an arrest may occur, of course, under many other conditions, but as one symptom among many it is worth mention; it is not, however, invariable, depending as it does on the seat and extent of the inflammation.

A very remarkable outcome of pericarditis, as has been seen, is angina pectoris, real enough. Stokes was, I think, the first to describe this complication, a very grave one not only in respect of the suffering, but as possibly mortal. Andral also, in 1834, published three cases, and Sibson four. The symptoms may amount to no more than a substernal oppression; but in some instances, rather suddenly, a tearing or vice-like pain arises behind the sternum, not aggravated by pressure, and boring to the left. Numbness and pain may extend to the arm, the face be pale and pinched and the extremities cold. The pulse is affected only so far as may be due to the primary conditions. In my work on "Diseases of the Arteries" I have given this explanation—that the attack depends upon an extension of the inflammation to the overlapping limb of the pericardium upon the aorta, and its penetration into the sensitive adventitia of the vessel. It is perhaps most apt to arise in the pericarditis of rheumatic fever, in which malady, indeed, the inflammation may spread inwards from the aortic area of the endocardium to the great vessel itself and its outward coat. Adami says that at necropsies old adhesions between the pericardium and the aorta are not uncommon. Peters and others have attributed this angina to extension of the pericarditis to the nervous plexus of the heart; but, as I have pointed out (loc. cit.), these ganglia are motor in function, not sensory. This angina, although belonging to the hopeful side when the patient is young, may be mortal because the benefit of age may be lost in a subjacent myocarditis, or under an effusion no less menacing. In some cases of aortitis a dry pericardial rub has been detected about the base of the heart. Embolism or thrombosis (*e.g.* syphilitic) of a coronary branch may be attended with epicarditis, and possibly, therefore, with angina pectoris.

The respiration will vary with the variation of the series of changes of which it may be a part. For instance, in the pericarditis of Bright's disease seizures of dyspnea of great intensity may attack the patient, but be due rather to the uremia than to the state of the pericardium. So in effusions the respiratory symptoms will vary with the rapidity of the effusion, the pressures on the auricles, the pulmonary collapse, and so forth. Apart from these and such larger causes, in mere pericarditis the breathing may be little affected; but a persistent distension of the alae nasi should not escape observation. Moreover, among the freaks of pericarditis, alterations of the voice have been recorded; Sibson indeed mentioned a case in which implication of the recurrent nerve produced aphonia, and like instances have been recorded by Stokes and others. The use of the laryngoscope would rarely be practicable in such cases.

The urine in acute pericarditis is that of other pyrexial conditions; the appearance in it of albumin would usually be due to the primary infection; but in renal pericarditis albuminuria would of course be a part of another story.

Physical Signs of Acute Pericarditis

Inspection will reveal little save in young persons in whom a pericardial effusion may bulge the wall of a supple chest, for the cyrtometer may show a bulge in the transverse section; the left mamma may be a little higher than the right; the spaces may be filled out; and little more may be learned by palpation. Still it is of much importance to ascertain, if possible, the spot of the apex beat, as in the course of the disease this may be displaced or suppressed. The heart and its content being of higher specific gravity than the effusion cannot float up but is pushed up. Fremitus—a purr or creak—may be felt on firm pressure in the mid-area of the precordium, rarely in ordinary pericarditis, more frequently in that of Bright's disease. Some authors describe under the hand a sense of an undulating beat—"the crawling beat"—a transient, and I think rare, phenomenon, due perhaps to stretched intercostal muscles and spaces. For me it is only hearsay.

Percussion tells us more, though too often with an uncertain sound. In a dry pericarditis we cannot expect that percussion can help us much; when effusion begins it may help us more than any other means, but not always decisively. The list of the fluid this way or that seems to follow no uniform rule; sometimes it presses forward, sometimes so far backwards as to elude our touch. Cabot thinks that 150 c.c. may be detected. I suspect in the adult it requires twice that. Ordinarily we find that it presses forward, and so pushes the lung aside as to enlarge the transverse trapezoid area of dullness; then, rising higher, it pushes the apex of the heart also upwards. Thus the area of deep cardiac dullness enlarges to that of the superficial. As the effusion exceeds, say 150 or 180 c.c. and more, the lungs recede, including, if it be free from adhesions, the lappet of the left lung which embraces the inferior angle of the heart. Thus the area of dullness, at first extended chiefly transversely beyond the right sternal border, may there extend itself up to the fifth or fourth right space, even to the right mammary line; and, on the left, even to the second space and the left axillary line; but this would signify a very large content, say 500 or 600 c.c. or more in the adult. I have heard of the apex of the left lung being thus thrust out above the clavicle. Emphysema or other alterations of the lung or pleura, or adhesions would of course modify these signs. But ordinarily the full pericardial sac assumes a pyriform rather than a globose shape with the apex upwards. Not only so, but if fairly full and free to assume its common form, its diagonal to the left is notched, as Sibson pointed out, by an angled depression, so as to present the shape of the "brioche" to which Potain likened it; that is, the downward curve to the left shows a depression or nick about the junction of its upper and middle thirds. The cardiohepatic angle is much enlarged. But characteristic as this shape of an effusion of 420 to 460 c.c. may be, in practice we find that we cannot wholly rely on such demarcations; the evidence of percussion must be taken with the other indications. The reader familiar with rheumatic fever knows well how variable is the form of the heart in myocarditis, how in the daily tides of the disease it will dilate, and again come back towards its proper limits as blood pressures and elasticity of tissues and reflexes vary. The heart may dilate as rapidly as effusion may increase. Position may make some difference in these features of percussion; thus the heart's beat may become perceptible as the patient leans forward, or the outlines of the dullness may vary likewise. But a more troublesome variation is the inclination of the fluid backwards, whether by the presence of adhesion, the form of the heart, the collapse of the lung, or other variation in the physical conditions not yet fully comprehended. Then dullness may be detected below the apex beat which may rise even to the third space, and, if the effusion be considerable, a patch of dullness may be found posteriorly under the angle of the scapula, associated with a tubular quality of breath sound; these signs, which, if to be credited to Pins of Vienna, were well described by Dr. Ewart, I have found invaluable in effusions, serous, purulent, or hemorrhagic. It is said that Ewart's signs appear only in children; this is by no means the case; I have obtained them repeatedly in adults and in quite old people. They have even been taken in error as indications for tapping the pleura (Ashby). They disappear, of course, or are modified if the lung collapse or be displaced. This dull patch may be reduced and the apex beat restored if the patient leans forward. It is said that they disappear in the hands and knees position, but I have never felt justified in imposing such contortions upon one suffering from so great an affection of the heart. We shall remember, in comparative observations, that, as effusion may reduce, so dilatation of the heart may prevent a definite reduction of the dull area in front, though in my experience the note of cardiac dullness is not so wooden as that given by substernal fluid or solid. The dullness of mediastinal growth occupies a different area. The liver may be depressed if the effusion be copious.

From the evidence of percussion we pass on to that of *auscultation*; and begin with a dry pericarditis, or the stage before much transudation has taken place, states in which a friction sound may be heard and less frequently felt by the hand. It is obvious that as effusion takes place, and the coats are thus separated, friction of one upon the other is prevented. Friction then may be harsh and persistent or elusive and transient, so that from its absence little or nothing can be inferred. When present it is easy of apprehension, though variable in quality, position, and degree. It has been compared with creaking leather, with rustling silk, with crackling parchment. How, then, can it be easy of recognition? By two of its properties, namely, its striking superficiality, and its cross times with the valvular sounds. The rub, single or double, is around about these sounds rather than coincident with them. If complete it consists of three parts—the systole of the auricle and the systole and diastole of the ventricle. Moreover, on shifting the stethoscope the rub obeys none of the boundaries nor the lines of propagation of the valvular murmurs. Inconstant as it is, yet it frequents the middle and basic areas of the heart centering usually about the second and third intercostal spaces and neighboring sternum, and, being conducted beyond its primary seat, ends here; this seat may, however, be a wide one; it may sound over the whole of the chest, or at the xyphoid, dying out towards the apex; occasionally in a rheumatic case it may be heard behind, especially if the left lung be collapsed and the heart large; not so rarely in Bright's disease, in which the rub is apt to be harsher and more persistent. The intensity of the sound is no guide to the degree of inflammation; in Bright's disease the patch is often a small one, and more or less stationary. The friction sound may be increased by pressure with the stethoscope, especially in the softer chests; or may vary with change of position, such as leaning forward, or from hour to hour, or again with the respiration, increasing on deep inspiration, sometimes on deep expiration. Endocardial murmurs are not often thus distinctly reenforced. It must be remembered, however, that the protruding lappet at the anterior inferior angle of the left lung, already mentioned, may be the seat of a pleurisy, and, if so, may give rise to a friction modulated by the rhythm of the heart. If, as occasionally happens, the pleura be adherent so that respirations do not affect the rhythm, the distinction between the pleural and pericardial friction sound may, unless there are other determining facts, be extremely difficult. But if the patient holds a deep breath, the result should be helpful if not decisive. Before the rub is heard, it is said, and I think truly, that a gallop rhythm, or tumbling of the heart may be heard, especially about a rapid heart, due presumably to a sticky action of the coats of auricle and ventricle. Potain attributes it with little reason to a flopping distension of a lax myocardium, or sometimes perhaps to the one cause, sometimes to the other. It is true that on palpation before effusion such a flopping action of the heart may sometimes be perceived. It is said that in a dry state of the membrane a pericardial rub may arise without pericarditis, as in cholera; or again, in slight hemorrhage, or even about a hypertrophied heart: of the first opinion I can say nothing; from the last two I differ so far as under such chance conditions one may venture upon an opinion. It seems fairly certain that the white patches do not set up any audible friction.

As effusion is poured out, unless it be retrocardiac, possibly held back by an adhesion, the ordinary heart sounds grow dim and the rub begins to fade; it may survive for a while here and there, as about the base, coming and going, but as the effusion increases it finally disappears. The percussion tests, already described, are now required, or, if the effusion fall backward, X-rays may reveal it. Usually, in rheumatic fever, after reaching a certain fullness, the transudate is reabsorbed, leaving the exudate to pass through its retrogade stages, sometimes with a return rub. This *frictio redux* is less regular than might be expected. Care must be taken in regressive cases to distinguish between fluid and dilatation of a poisoned myocardium. The percussion area may vary as the patient leans forward. The behavior of the veins of the neck does not help us much, nor does the pulse, though the venous pulse, the jugulars filling in inspiration, should return. A waning pulse, seeming irregular or even impalpable, may be due to compression of the auricles, or to myocarditis; in my experience the leading difference is that the dull area of the dilated heart of myocarditis varies not a little if it be watched from hour to hour, or day by day; that of fluid does not fluctuate to and fro. A radiograph would help to solve the difficulties. As the fluid recedes, the heart sounds, normal or abnormal, should reassert themselves. Heart block, degrees of which have been recorded in pericarditis, is probably due to concurrent foci of myocarditis.

In cases of coexisting empyema of pericardium and left pleura, no uncommon but a very mortal condition, direct distinction of the pericardial empyema is often impossible unless by exploration after resection of rib; this likelihood of the combination must, therefore, always be borne in mind and search made for it. Like a pleural empyema it may burrow in almost any direction, not to an intercostal space only. Conversion of a serous into a purulent effusion may not be betrayed by a change in the temperature curve, but is to be suspected if the quantity be large, for it always is copious, sometimes enormous, and the general condition of the patient suggestive of a mixed infection. A rheumatic effusion, unless accidentally tainted, is probably never purulent. The exploring needle would thus settle the doubt. A purulent pericarditis is generally such from the outset; and often is secondary to a pleural empyema, or a costal osteochondritis, and so on. I may add that in differential diagnosis of pleural effusion I have long found "Grocco's triangle" an invaluable aid.

The backward pressure of the pericardial fluid, whether serous, purulent or hemorrhagic, arresting the lower part of the left lung causes it to collapse; thus dullness and in an incipient stage imperfect air entry, Skodaic resonance, or bronchial breathing may be found. An atelectasis here may be taken for an accompanying effusion into the left pleura, and an exploratory puncture made in vain. A careful survey of the whole case will usually avoid this error. The formation of adhesions and its effects we will consider presently.

Diagnosis of Acute Pericarditis

The *diagnosis* of acute pericarditis is for the most part expressed or implied in what has gone before; but a few points may be indicated. The friction sound may seem for a moment to be hardly distinguishable from an endocardial bruit; but a little discrimination will suffice probably in all cases, to decide the problem. A due comparison must be made of the maximum points and the conductions of the sounds, the exocardial riding over, rather than coinciding, with the endocardial and seeming much nearer to the ear. Endocardial murmurs again are less variable in quality, place, and time; though it is true, consolidation of the lung near it might carry the friction sound beyond its ordinary limits. No endocardial murmur springs up suddenly full grown. There may be more difficulty when pericardial and endocardial murmurs arise together, especially if the endocardial be the louder, but even then, on the rules already mentioned—stethoscopic pressure, time, rhythm, effect of respiration, etc.—discrimination ought not to be out of reach. The difficulties are greater when left pleural and pericardial effusions come together; sometimes indeed, as I have said, a pleural effusion may simulate pericardial. Yet it will be found that error is apt to creep in, not so much for lack of criterions as for lack of apprehension; from forgetfulness that in certain conditions pericardial effusions are apt to arise and to run their course insidiously and silently. Let the possibility of pericardial effusion be remembered, then its detection will be feasible enough, for even if the effusion lie posteriorly, the patch of dullness and bronchial breathing under the scapula should reveal the condition. Notwithstanding, as I have said, a coincident left pleural and pericardial effusion may be distinguishable only by puncture or radiograph, or perhaps by displacement of the heart to the right. Here again, however, the secret is to be on the lookout for the pericardial factor. It is true no doubt that some of these diagnostic points depend on more than one examination, on the comparison of repeated observations, so that a consultant, seeing a case once only and without an X-ray picture or perspective of the previous changes, might for the moment find decision difficult. The gravest diagnostic decision is that between pericardial effusion and dilatation of a relaxed heart, the burden being the greater when puncture of the pericardium is in question. He who has watched the case will have noted, as I have said, the changes of the heart's diameter from day to day and Abram's reflex[1] may be obtained. Failing this advantage, the posterior signs should come to his aid, for puncture will not be proposed unless the effusion be so large as to give rise to these posterior signs. A hypertrophied heart is more easy of diagnosis by the downward pointing of the apex of its triangle, the character of its sounds, the history of the case (valvular or nephritic), and so on. The action of the heart, disordered as it may be—anapaestic, dactylic, and so on—gives no distinctive information; but we remember that in an acute case by myocarditis, in an old case by fibrotic invasion, the heart may be of low potential. Fullness of the liver would generally point rather to compression of the auricle than to myocardial failure, unless, of course, in a case of old valvular disease.

The *roentgen picture* will not reveal pericardial effusion until it is copious enough to be mapped out by percussion; but then it may show still better the gourd bottle or "brioche" shape of effusion as compared with cardiac dilatation. It is said that in some cases the heart may be seen in the midst of an effusion as a dusky body surrounded by a clearer shadow. Adhesions are not very well defined by the X-ray, as the cardiac outline is not always uniform, save at the base of the chest, where firm and thick adhesions of the pericardium to the diaphragm may be distinguished, partly by the shadow, partly by the behavior of the organs; the diaphragm does not draw away from the heart, the left half of the diaphragm is immovable or nearly so, the angles between the heart and its floor are filled up, and the edges of the sac are not sharp but shade off to the lungs. With adhesion, the heart's outline becomes blurred, as often indeed with an exudate; and the heart may be distorted or thrust out of position. The left pleura or the mediastinum, may of course be implicated in the mat. Mere dry pericarditis makes no shadow. Mediastinal growths or aneurysm I have never found to simulate pericardial effusion; the history of the case, symptoms, and seat of dullness, the pressure signs, and so forth, have made distinction comparatively easy. The two main maxims of diagnosis are to consider the history of the individual case, and not to forget to keep in touch with the state of the pericardium.

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[1] Abram's reflex is the decrease in the percussion area of the heart which occurs if we chafe the cardiac area with a towel or india rubber glove.—Ed.

Prognosis of Acute Pericarditis

Of the course and prognosis of pericarditis no general notions can be given, as it is rarely, perhaps never, a self-contained condition; acute pericarditis, if rheumatic, is practically always associated with myocardial and valvular disease; in other cases renal or other complications dominate the issues. Or an acute pericarditis may subside into a chronic state, extensive adhesions may form, and embarrass or even throttle the heart by a complete synechia. If chronic from the outset it may be due to some general toxic condition. A simple rheumatic pericarditis may run for three weeks, and if it subsides without large adhesions, may pass off harmlessly; indeed it is ordinarily the least menacing of the inflammations of the heart, and we perceive more or less orderly regression of the symptoms and signs we have described. In Bright's disease pericarditis is bad rather as an omen than as a peril.

Treatment of Acute Pericarditis

The treatment of a case of pericarditis depends in the main upon the nature and associations of the particular case. In an ordinary serous pericarditis, forming part of an attack of rheumatic fever, the means taken to combat the primary disease will suffice for the pericarditis. The effusion, as a rule, does not increase beyond the limits of safety and is reabsorbed without the aid of the physician. Nevertheless, I am bound to say that the application of an ice bag to the precordial area, although ventured upon with some misgiving, seems to be harmless, to moderate the local discomfort, and to calm the action of the heart. Nevertheless, it raises the blood pressure by vasoconstriction—probably by some 50 mm. Hg.; so that if myocarditis be present in a larger measure than just subjacent to the visceral pericarditis, the ice bag might put much stress upon the heart. In rheumatic cases there is always some myocarditis, but it may be only in minor degrees and focal. Whether the ice bag shortens the course of the inflammation or not I cannot say, but it is worth doing and is comforting to the patient. The ice should be broken small, and the bag, wrapped in flannel, so far supported by a cord to a bed cradle that its weight does not oppress the patient. Two bags should be at hand so that as the ice liquifies alternations of the bags can be made without delay. During long sleep the bag should be removed. I now prefer the ice bag to blisters, leeches, or other local application, unless the pain be troublesome; in this case, as in a pleurisy, I apply leeches, which nearly always give permanent relief.

Of salicylic ionization in rheumatic pericarditis (Macintosh) I know nothing.

In the acute pericarditis of rheumatic fever *operative measures* are rarely needed. The effusion rises to a moderate bulk and then subsides "of itself," or may be hastened away by a few light blisters. Sometimes, however, it persists without abatement for three or four weeks, or by its increase it imperils life by pericardiac pressure, and tapping is required. The pulse may become small and weak, and dyspnea and faintness may be ominous. My first case of this degree was in 1866, in a young man the victim of rheumatic fever. I was called to him in the middle of the night and found him almost syncopic, with a large pericardial effusion and rising venous pressures. As an ardent pupil of Trousseau, whose operative treatment for empyema I had been already carrying out in the Leeds Infirmary, I was ready for this occasion, ready as far as to send for my colleague, Mr. Wheelhouse, who punctured the sac in the left costosternal angle; the fluid issued in strong jets with the heart beat, giving almost instantaneous relief to the sufferer. He recovered quickly from the pericarditis, no second tapping being needed, and returned to work in due course, though with a heart internally damaged. If the exudate be purulent of course the sac must be incised, either outwardly, or, in the case of an associated pleural empyema, through this cavity. The surgical measures will be found described in books on surgery; here it is sufficient to say that most operators now prefer to puncture in the epigastrium (Marfan's point), feeling for the point of the xyphoid and bewaring of intestinal tympany, though others prefer one of the left intercostal spaces (on the right the pleura may be punctured), generally the fourth or fifth some 4 to 5 cm. from the sternal margin to avoid the mammary artery. The objection of this position is the shallower layer of fluid, and the danger to the heart, so Tessier prefers the seventh. Clinton Dent used to recommend incision even in serous effusion (in purulent effusion it is of course imperative). By dissecting down to the sac the mammary artery, which runs just outside the left border of the sternum, is easily dealt with, the sac entered with confidence, and can readily be reopened if the fluid reaccumulate. In this way, too, the encircling lappet of lung is surely avoided. In puncture a thick pericardium or membrane may block the entry of the trocar. If a skin incision is made before puncture, which it is well to do, the skin is drawn down so that it may slip back and cover the puncture. Press the point of the trocar slowly inwards, withdrawing it in good time and let every delicacy of touch be used so as to beware of entering the cavity and of touching the heart when the point of the cannula, hitherto at right angles, should be dropped and turned a little to the left. To touch the heart with the trocar is harmless, and even to prick it does no harm. No aspiration is needed. If the tube be blocked, turn it a little upwards and then push up the trocar. Let the fluid which, if actually from the pericardium, not from the pleura, will issue in jets, be carefully noted; if the slightest opaque, be sure that it be examined at once for pus, for, if the least degree tainted, the track must be laid open, a rib perhaps resected, and free incision made, lest the track and perhaps the pleura be affected. Many cases of purulent pericarditis have done well after incision and drainage, as reported by Dr. Samuel West and others, especially in war surgery, but much depends on the nature of the particular case and most of them are of a grave or even desperate kind. Now and then from the post-mortem room a case is recorded of a pericardial empyema which, undiscovered during life, has dried away into a caseous or glutinous degeneration and obliteration and succeeded in a sort of recovery. Injections, whether of air or liquid, are never to be used; such disturbance has caused arrest of the heart.[2] A drag on the membrane is thus perilous.

Of medicinal treatment, apart from that required by the specific nature of the case, not much is needed. If the urine be in normal quantity, no diuretic is required; no diuretic will touch an interpericardial effusion. The patient will find relief if lifted from recumbency towards the left side; thus pressure is taken off the lungs. It is important also to check any cough by anodyne linctus. Diuretin may be added to the usual anti-pyretic salines, and a little Dover's powder with or without the addition of a little gray powder is often useful. If the inhalation of oxygen be prescribed let it be done early in the illness, not kept back as a viaticum.

Needless to say the patient must not stir for any purpose—food, urine, or stool. Let the motions be made as easy as possible by such means as sulphur (compound liquorice powder), tamarind, senna electuaries, or glycerin enema. Cooked fruit may be included in the diet. The diet should be that of pyrexia, modified so far as necessary by the needs of the primary malady. If tea is given it should be sparingly, and well diluted; coffee should be withheld. The advances to convalescence must be regulated rather by the inferred state of the myocardium than by that of the pericardium. To get the patient about early to prevent adhesions seems to me a shallow notion.

The treatment of the pericarditis of Bright's disease, so far as any there be, is that of the primary malady; and it will not be forgotten that pericarditis may arise in the nephritis of scarlet fever. For the treatment of myocarditis and other cardiac symptoms in these cases the reader is referred to the proper chapter on the subject. Angina pectoris must be combated by opiates, perhaps by nitrites, and the heart protected from vagus arrest by atropin.

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[2] See note on such arrest by pleural injections, Allbutt, "Diseases of the Arteries", 1915, Vol. II, 479.

TUBERCULOUS PERICARDITIS

Tuberculous pericarditis as a post-mortem discovery is not very rare; in most cases it is a late term of a long series, and provokes no manifest symptoms. It is late because the pericardium is less rich in blood supply than the parts which take the disease sooner. Tuberculous pericarditis then is of little clinical importance unless, as in a certain proportion of cases, the effusion rises to a high tide; then it may attain a bulk as high as in any other disease, if not higher. Some of the "record" effusions have been tuberculous (Byron Bramwell). It occurs at all ages, most frequently perhaps in youth from the age of five to fifteen; but it may occur in adults also, even of healthy aspect, and again, cases in infancy are on record. It is more frequent in the male sex (Osler). It occurs also in animals.

It is said that the pericardium may be a primary seat of tubercle, which doubtful proposition, as it seems to be, is supported by Virchow; usually it is secondary to tubercle of the tracheobronchial or mediastinal glands (Osler); but it may likewise follow pulmonary phthisis and may extend from the pleura, or pass by the lymphatic channels. It is ordinarily a chronic process, but may form part of an acute outbreak of tubercle in several serous cavities, or of a general miliary invasion. The effusion may be large, yet generally it is moderate in quantity and follows an eruption on its inner surface of small gray granules, each surrounded by a hyperemic zone, or it may be "dry." In chronic cases the inflammatory deposits are apt to be very thick, and, if time be given, to end in synechia and callous mediastinitis, or in partial adhesions with exudations in their interstices, serofibrinous, glutinous, fibrinous, purulent, or perhaps ultimately calcareous. The blood vessels seem to be weakened, as tuberculous effusions are often sanguinolent; indeed, such an effusion suggests tubercle. The thick false membranes lie in villous layers under which are seen the cheesy foci which are the coalescence of the nodules and hemorrhages. Peter (in Charcot's System) gives a full description of the pathology of these cases; he says that the tubercle, if it penetrate somewhat into the myocardium, does not go far—this tissue has no great disposition to receive it—but turns fatty under the interference. Tubercle bacilli are to be found in the membranes and in the effusion, and about the epicardial vessels, but not uniformly distributed, and may be in colonies not readily detected. Anasarca, if more than anemic, may point to embarrassment of the heart, and a copious effusion may set up a dyspnea more severe than the other conditions fully explain. The diagnosis must be almost entirely by the physical signs which have been described already.

Constitutional treatment of tuberculous pericarditis must be merged in that of the whole malady; but if the effusion needs tapping, the disposition to purulent change is not great. But a blockage by fibrinous layers and clots is apt to be troublesome. It may be well to resect a rib. Repeated tappings may be required (Symes).

PNEUMOPERICARDIUM

Pneumopericardium (pneumotosis pericardii) must, I suppose, always be associated with effusion, usually with pus. It must be a rare condition, though perhaps more often met with in surgical than in medical practice.

In one or two cases I vividly remember the strange sounds characteristic of this condition, which, once heard, are very striking to the ear. The plunging of the heart in the air and fluid of the sac—for of course fluid, serum, pus, or blood must be present—causes a continuous rotatory splashing, well likened to the wheel of a water mill. The condition, unless it be in military surgery, must be very rare, a rare accident arising from such a cause as a fractured rib entering a lung and passing on to the pericardium and carrying air with it. Or a fistula may form between a pulmonary, possibly gangrenous, cavity and the pericardium, a diseased gland may eat into it, or again an ulcer or the like may by perforation admit air into the sac from the stomach or esophagus; and cases are on record in which an anerobic organism, such as the bacillus of Welch, has generated a gaseous putridity in the sac. Surgical emphysema may be associated with the pericardial turmoil arising as it does from similar causes.

Such being the manner of lesion the attack would almost always be sudden and painful—a violent substernal pain, with oppression, palpitation, dyspnea, and a failing pulse. The air, if under pressure, will push aside other parts and gather at the top of the sac, if the patient be sitting upright. Percussion will give a tympanitic metallic timber, best obtained with a pleximeter, varying with posture; likewise a variable level of fluid may be made out. The murmurs of other outer and inner sounds of the churning heart are very variable, as are the causes and effects of the lesion. Sometimes "metallic tinkling" may be perceived, and, as the fluid escapes, frictions may become audible. Some of these sounds may be heard by the patient himself. I have seen two cases of hernia through the diaphragm on the left side. Both were readily diagnosed, and there was no simulation of pneumopericardium and little of pneumothorax. Borborygmi in no way resemble the splashing of a cavity.

There is no fear of overlooking this state of things, and the diagnosis cannot often be doubtful. Tinkling might be heard in the stomach, or in a large contiguous pulmonary cavity. A flatulent stomach underlying the heart is apt to give a metallic timber to its ordinary sounds. Pyopneumothorax could hardly simulate the continuous churning, and changes of posture should give some help. The X-rays might illuminate the disorder of the injured parts, but, so far as I know have not been applied. In cases of wound, recovery might come about; the treatment, wholly surgical, would depend upon the other elements of the particular case.

Hydropericardium

Water does not gather in the pericardium so frequently as in other serous cavities. It may be due to local causes, such as pressure by tumors; or again to cardiac or pulmonary diseases or emphysema; more often to general causes, such as renal and other cachexias. It is apt to concur with or follow hydrothorax. Colonel McGarrison found it in thirteen per cent. of cases of polyneuritis gallinacea, due to specific food deficiency. The normal content may be about 15 c.c.; certainly more than 45 c.c. would be regarded as morbid, but might be a part of the process of death. In disease, as we have seen concerning tuberculosis of the part, the collection may be prodigious, even to 1,000 c.c. or more. Unless colored by blood or hematin it should be a clear, limpid, yellowish green fluid, which may contain various chemical ingredients in solution, such as urea, bile, etc. Sugar is said to occur in some effusions of non-diabetic cases. The albumin content will be small, and the cell content still less. The serous membrane is usually slightly opalescent, pale, and thinned by stretching; and the subepicardial layers of the myocardium may show marks of deterioration.

In respect of physical signs we have said that not less than about 90 c.c. of fluid can be detected by percussion. Friction is, perhaps, never audible, but on the other hand, as there are no adhesions, the levels of the effusion and posterior signs are more obedient to changes of position, respiration, and so forth. There is no fever, no pain. In a word, as I have said of other pericardial states, diagnosis is by vigilance in cases where this sac may be affected, as for instance in case of dropsy of limbs and other cavities. Treatment must depend entirely on the concomitant conditions, unless tapping may be required; in this case the operation is the easier as the effusion may be more copious, and free from imflammatory or septic qualities. In such vigilance percussion behind must not be omitted, nor listening for bronchial breathing or signs of pulmonary collapse.

Hematopericardium

By this title we mean not merely an effusion more or less mixed or stained with blood, or the brown coloring matter of hemolysis, but a bleeding into the cavity. Possible imbibitions after death will not be forgotten. The commonest causes are, so I guess, rupture by some invading disease, as of an aneurysm or a wound from without, or rupture of a coronary artery, or possibly—so it has been said—of a death by suffocation. If the effusion of blood be rapid, death is of course almost instant; but as in the case of rupture of a small coronary branch, the bleeding may be slow enough to amount to 500 c.c. and yet death may be kept at bay for awhile. In this case dizziness, pallor, syncope—possibly convulsion—may point to the kind of event, and diagnosis will not be difficult. If an aneurysm attaches itself to the pericardium, rupture into the sac may well occur and is not very rare; but in these cases such an event is more or less expected, as it might be in a cachexia, such as scurvy. As a cause of sudden death in persons apparently in usual health, rupture of a coronary branch is to be thought of when an internal bleeding is indicated. Then the pulsus paradoxus, the subscapular dullness and bronchial breathing, which twice I have verified in coronary rupture, will point to the cause. In one of my cases, that seen with Dr. Humphry (p. 262), the pulsus paradoxus appeared first on one side only, but became bilateral after the lapse of a few seconds. It is scarcely necessary to say that tapping the sac for a bloody effusion is out of the question. It is conceivable that from a moderate bleeding the serum might be drawn off if the patient survived, but such an issue is too unlikely to need discussion.

Symphysis or Synechia Cordis

When by adhesion of the two parts of the pericardium the cavity was obliterated it was supposed in times past from Galen onwards that the patient had been born without this investment, that he was the subject of a malformation (Chase). It is true that such a malformation may occur; Faber has summed up the records on this subject. The deformity of ectopia cordis is usually without pericardium, but in the large majority of like cases the absence of the external coat is apparent only; as Lancisi pointed out, and Baillou after him, the two coats have been glued together by an inflammatory process which may cause now a partial, now a universal adhesion. Partial adhesions may be of slight or no importance, may be a mere post-mortem incident; Adami says in 3.5 per cent. of all necropsies. A universal or very extensive adhesion, no very rare event, is a much more serious matter. Partial adhesions, as already said, may form lesser sacs containing more or less noxious remnants of effusion ("cloisonné"), of course a mischievous event sometimes ending in a calcified layer. Ossification has been recorded. Ordinarily the adhesions form harmless bands or patches which do not interfere with the cardiac functions. Sometimes clots of fibrin or a detached band may run loose in the sac, as it were a "loose cartilage" in the cardiac joint; happily the heart does not trip over them. It is supposed that the movements of the heart prevent, or limit and probably always stretch these adhesions, especially about the mid and apical parts of the heart; partial adhesions being more frequent about the less locomotive base and roots of the vessels. But here we are to consider only total adherence by a dense fibrous growth which in its earlier stages may admit of some rending asunder; in its later, condensation brings about an inseparable fusion. We owe our earlier appreciations of this subject to the classical article of Potain in the *Clinique Médicale de la Charité*; since that day many studies of the subject have appeared, for example, by Skoda, Williams, Sibson, Aran, Traube, both on local and symptomatic features. A comparatively recent one is published by Smith, where the author gives the descriptions of sixty-two necropsies of the kind. Unfortunately statistics are vitiated by inaccurate record of the degrees of adhesion. It appears from these witnesses that the two chief inflammations which thus affect the heart are, as we should expect, the rheumatic and the tuberculous, both potent factors in the "plastic obliterative pericarditis" of Stokes. Or it may be in some cases due to a slow insidious irritation, still possibly tuberculous, propagated from neighboring parts. In some obscure diseases, especially in children, we find, as it were, a universal perivisceritis, the capsules of liver and spleen, etc., being also thus affected. The fibrosis penetrates more or less into the myocardium, so that on stripping the capsule the muscle is torn away with it; this penetration, following up a primary infection, and throttling the arterial branches, impairs the nutrition and quality of the heart, and sometimes leads to aneurysmal yielding of its wall.

In these large, practically complete adhesions the state of the heart is not constant; mechanical causes combine variably with the pathological. The prevailing event is hypertrophy and dilatation in various relative proportions. In some cases we are not surprised to find an atrophy. Much depends of course on the original infection and the age of the patient, disease of the endocardium, the patency of arterial channels, and so on. We find, accordingly, a like variability of symptoms. As we have seen in the active phases of pericarditis, the process of adhesive inflammation by no means always confines itself to the parts about the heart; if in some cases the outer pericardium is free, in others it is apt to spread to neighboring structures which lie about it—to the mediastinum, the chest wall, the pleura, the great vessels, the tissues along the spine, the left and middle diaphragm, and the pleura. Some leading authorities, such as Jaccoud and Durozier, consider that it is by adhesions to the pleura especially that symptomatic disorders and legible physical signs arise. A mere symphysis without sternal attachments may be of no great clinical importance; or again, with outward adhesions the heart may be free within, and no operation needed.

Symptoms of Synechia Cordis

Some time, some months, may elapse before any symptoms attributable to pericardial adhesion may appear; we know well how in the rheumatic fever of a young patient, subacute and chronic sequels may cling to him, milder phases of pyrexia, wandering pains, palpitations, oppressions of the breath, a dilated and atonic stomach, and so forth, being apparent while one cannot say what flax is smoking beneath; a smouldering myocarditis, pericarditis, mediastinitis, and the like. In these discomforts it may be difficult to interpret any in the sense of embarrassment by adhesion. Many months, nay years, indeed, may elapse before such evidence as this may end in obvious disease, and then perhaps indefinitely. But in the course of time when the fires seem to be extinct, beside such symptoms as may be attributable to inner cardiac lesions, or to other foci of tubercle, certain symptoms and signs may suggest, perhaps prove, not only a suffocation of the heart in its own investments, which, so some say, does not suffice to produce grave disorder, but also an attachment to pleura and diaphragm and possible strangling of great vessels and of the vena cava with consequent symptoms already mentioned, and others now to be described. The action of the heart may become more and more turbulent, dyspnea pass into cyanosis, the ankles swell, and the pulse diminish in volume and strength, so that heart failure of some origin is apparent. In my experience the most trying symptom in these cases is the wrestling of the heart in its bonds after a manner which perhaps may be called pathognomonic; a beating, struggling, bursting strife most distressing to the sufferer. But probably these fights are the efforts of a strong myocardium in a young person, and may be less manifest in the less capable hearts of older persons. This is one of the cardiac maladies in which the closing scene may end with some suddenness, especially if aortic insufficiency coincides with the other disabilities. It would seem that valvular default is apt to arise in these cases of synechia, as a so-called "functional" derangement, a derangement due to distortion of the heart rather than to static alterations in the valvular apparatus itself (Paviot and Froment) which may or may not be present. But on the other hand valvular lesions, such as mitral stenosis, may result from a tuberculous endocarditis (Barbier's case.)

Physical Signs of Synechia Cordis

The physical signs of synechia are fairly definite, although it may be that some of these cases are so far latent that they escape diagnosis during life; if so, the condition may not indeed be very serious. The fault of observers of these signs has been the desire to discover some one conclusive sign. Such definite indications are rare; in synechia, as in most other inner disease, we have to regard the case as a whole, comparing all the symptoms and signs and giving to each its due perspective. If this survey be made, the diagnosis of synechia will prove less difficult than the books suppose.

On *inspection* of the chest the heart beat may appear heavy and diffused, the chest wall may be thrust forward, or perhaps retracted and the abdominal breathing straightened. Much also has been made by Hope, and others since, and quite rightly, of a drag upon the precordial area by the heart bound to it beneath; and on account of the adhesion of the pericardium, the pleura, and the wall, there may be less respiratory excursion forward on the left lower chest. Wenkebach has made a careful study of the bearings of such conditions on the mobility of the tied diaphragm. I remember one case of arrested epigastric respiration and rhythmic systolic retraction of the lower ribs, in which the last five or six costal cartilages and the lower end of the sternum were bound down to the pericardium and diaphragm. A mere apical and limited retraction of the apex only must not be taken as peculiar to synechia; this may be due to some pull of the great vessels, or a local adhesion of the tongue of the left lung. On the other hand, it seems that there may be extensive adhesions of this kind without appreciable retractions. Much depends of course upon the precise mechanical changes and readjustments, and the relations of cardiac and pulmonary rhythms. A vigorous retraction may indicate a vigorous heart. Not rarely we find a "diastolic shock" due to elastic recoil. It is said that sometimes the heart beat in these cases is a roll or creep, suggestive of a revolution of the organ on its axis. Broadbent described, in a case with large adhesion to the diaphragm and a vigorous heart, a retraction of the tenth and eleventh spaces behind under the scapula.

Percussion is of no little service in this state; the impression given to ear and finger over all the deep cardiac area is very wooden, more so usually than is given by cardiac dilatation. Besides, the limits of the dull area are immovable; as Potain used to point out, there is no heart swing on turning from side to side, nor indeed any proper apex beat. This fixity to inspection and percussion is a very useful sign. Furthermore it is said that, if the diastole of the heart were checked by adhesions, a hepatic beat might be presystolic (Pezzi).

Auscultation, on the other hand, is not worth much in these cases, save of course for coincident valvular lesions, and possibly for some indications of myocardial work. The effect of extensive synechia upon the heart itself is not uniform. It is generally dilated and hypertrophied, in Potain's view, because, working in chains, it has so much more to do. Much must depend in the individual case upon the mechanics of the adhesion and on the condition, myocarditic, fibrotic, etc., of the heart itself. Speaking generally, the worst cases are the rheumatic. In tuberculous adhesion the heart, internally unaffected, may be unaltered in dimensions. Adhesions around the auricles may have, of course, untoward consequences. The value of the myocardium in young persons can only be roughly guessed at; response to digitalis may be of some assistance. Effort tests in these cases are rarely practicable or definite. It is said that in some cases of synechia creakings in the mat may be heard; of this I can say nothing.

The *radiograph*, on the other hand, gives very valuable testimony, often indeed conclusive. It is true that in the normal state the shadows of the heart and diaphragm may blend, but in many persons (seventy-five per cent.) on deepest inspiration a clear streak may be seen for a second or two between them. The patient should bend well to the left side, that the left lung may push the outer pericardium from apex to vena cava from behind forwards against the anterior wall (Czyhlarz). A negative picture is, therefore, of no service, but if the streak be positive there is no pericardial adhesion. In a definite case the ray picture will show an unmistakable dark extensive shadow in the area of somewhat triangular form with apex upwards and with a broad base. The heart is not always adherent within, and if it escapes may be free, whatever its internal injuries. The diagnosis then depends upon a summary of indications, and presents no special difficulties, if I may trust my own experience, which includes a few cases demonstrated by my colleagues and at medical meetings.

Prognosis of Synechia Cordis

The *prognosis* depends on two kinds of expectation—on the nature and complications of the individual case, and on the promise of operation. The complications, especially in rheumatic fever, may be grievous, or the pericarditis may be a part of a tuberculous process which will not wholly die out, or again of one of those smouldering chronic inflammations of unknown causation which may pass through many phases before becoming extinct. In consultations about operation these constitutional alternatives must be carefully considered, *e.g.* a large liver may be "cardiac" or may be due to more general causes; an operation can indeed be rarely indicated until the underlying invading process is at an end; nor would it be readily undertaken if symptoms of heart failure, such as dropsy, possible strangling of the vena cava, pulmonary and hepatic congestions, albuminuria, and so forth had appeared. So far as I have seen, operation is to relieve the painful mechanical stresses upon the patient; not much relief of heart disease can be expected. Still, in not a few cases, by setting free some of the bonds, both comfort and prolongation of life may be obtained in substantial degree.

Treatment of Synechia Cordis

Apart from the therapeutics of cardiac disease, which are dealt with elsewhere, that of synechia is summed up in surgical means (cardiolysis). In many able papers from 1903 onwards Brauer has taught the method and the advantage of his operation. It is well to remind the reader that much cannot be expected beyond relief of adhesions to the anterior wall. Here three to six costal cartilages and ribs may be resected so as to give space, and a more elastic cage, to the laboring heart; a relief indeed which patients gratefully recognize. The deep periosteum is hard to excise and may be left, taking the chance of any regrowth of bone. The technique of this and other such operations will be found in books on surgery. In too many cases, however, the adhesions, as we have seen, extend to neighboring parts outside the sac and set up more or less widely the so-called callus mediastinitis, involving the anterior chest wall, lungs and pleurae, diaphragm, aorta, vertebral column, etc. These conditions may be suggested by the ordinary physical signs and pulsus paradoxus, and filling of the veins in inspiration, though both of these phenomena may be produced by large effusion.

Neoplasms and Other Rare Conditions

Neoplasms of the pericardium are rare; they may be primary or secondary. *Cancer* as a primary invasion is very rare, a few cases only having been recorded, and these doubtful; even as a secondary deposit it is very uncommon; it may be metastatic, but more probably due to propagation from a neighboring seat of the disease, such as esophagus, rib, or skin. The neoplasm may be in nodules or diffused about the walls of the sac. In a suspected case enlargement of the subclavicular and other glands would be looked for. The effusion, whether inflammatory or dropsical, would probably be sanguinolent or purulent. I have tapped the sac in two cases of pericardial dropsy with malignant disease in or near it, with temporary relief. Broadbent described a *sarcoma* of the pericardium in a man aged twenty-three (see also Williams). But I need not pursue the search for pathological curiosities any further, unless it be to allude to Timme's case of hemangioma pericarditis, discovered at necropsy with some effusion (size 75 cm.). Pericardial hydatid (F. Dévé, 12 cases) must be only a post mortem discovery; it is a condition of long continuance which during life could scarcely be guessed at, though often attended with chronic adhesive pericarditis; so also for trichina or cysticercus, and occasional foreign bodies, such as needles. Syphilis of the pericardium, unless it be by some extension from the heart to the visceral portion, is rare perhaps because of the less vascularity of the part, and even if present, say in five per cent. of cases of cardiac syphilis, is only fibrous, not gummatous (Gibson, Babcock). Diagnosis is impossible. Bacigalupo has recently published a unique case of congenital mucodermoid cyst almost free in the pericardial cavity. It had some adhesion to the great vessels, a fetal inclusion at the level of the third or fourth branchial fissure. Actinomycosis may extend to the pericardium.

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CHAPTER X

THE CIRCULATION IN INFECTIOUS AND TOXIC PROCESSES INCLUDING ACUTE ENDOCARDITIS

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Introduction

It is generally accepted as axiomatic that the heart may be affected in all acute infectious and toxic states. The terminal phase of every fatal process of acute poisoning is marked by abnormal rate and sometimes by abnormal rhythm of the heart's action, followed by gradual decline in the efficiency of the circulatory apparatus. But the term "cardiac failure" is employed in a loose and indefinite sense in these conditions; it is used without reference to other factors which may be determining the issue, and without recognition of the fact that, in the great majority of cases, the cardiac failure itself is but an expression of general organic dissolution. In the terminal phase of pneumonia, for example, every system of the body has been poisoned by specific toxins, by vicious products of abnormal metabolism, and by deprivation of a normal oxygen supply, and failure of the heart is usually not the cause, but a sign, of death.

In approaching a problem of this nature, it is necessary to consider as a preliminary step, the contribution which pathological anatomy can offer to its solution. Is there any evidence that the disordered function of the circulatory apparatus has an explanation in structural degeneration? Does the cardiac muscle or extra-cardiac system or the regulatory apparatus show anatomical evidence of disease which, by itself, may be reasonably held to account for circulatory failure? Is there, anatomically speaking, any distinguishing feature of the circulatory system which is peculiar to individual infections or intoxications, and if so, what are these features and to which specific diseases do each belong? An attempt will be made to answer these questions in the light of a short review of the main pathological changes of the most common infections and intoxications which are supposed to involve in their progress a disability of the organs in respect to blood supply.

Of the greatest importance in dealing with this question, is a recognition of the fact that the heart is only one part of the circulatory apparatus. It is of course, the central and most highly specialized part, and in this respect is peculiarly vulnerable to toxic influences. Damage to its structure or interference with its regulation is incomparably more serious for the organism than any possible involvement of its auxiliary branches. But it is the whole vascular system and not the heart alone, which constitutes the organ of circulation, and in many acute processes it is impossible to estimate clinically or anatomically the extent to which the central organ, on the one hand, or its arborization on the other, is involved. This is neither the time nor the place in which to discuss the part played by the peripheral circulation in maintaining an efficient blood supply. It must be accepted as a fact that the function of arteries and veins is no mere passive one, although the nature and conditions of their propulsive activity may be complicated and obscure. It is sufficient for the present to emphasize the fact that patients who die with "cardiac failure" in acute infections succumb to toxic influences, which affect the heart, the peripheral circulation and regulating apparatus, and not only these but, in varying degrees, the nervous and respiratory systems. Assimilation and excretion may be perverted or diminished, and the lungs, kidneys, brain or alimentary tract may, in individual cases, constitute the main seat of reaction which determines the result.

The cardiac rate is, as a rule, affected in the febrile conditions. Physiologists state, and it is consequently assumed, that "the accelerated heart rate in fevers is due probably to the direct influence of the high temperature upon the heart itself." For the clinician the matter is not quite so simple. There are, of course, degrees of temperature which endanger life, but for practical purposes fever is regarded as a sign of disease just like a rash or a cough, and the feeling of fever of which the patient complains is a symptom just like palpitation or colic. In some fevers, for example in typhus and in pneumonia, the pulse is rapid; in others, such as typhoid and epidemic meningitis, the pulse is relatively slow. The pulse varies in fever, not according to the temperature, but according to the specific properties and affinities of the poisons which are generated directly or indirectly in the course of the infection. Marris has found that the slow pulse of the febrile stage of typhoid is not accelerated by atropine, thus distinguishing it from the pulse of many other diseased states, and also from the pulse of healthy persons. This discovery may or may not be of diagnostic importance, but it is of the greatest significance as indicating the possibility of ascertaining facts regarding the toxic influence of infections on the regulatory apparatus of the circulation. It suggests, if not a method, at least a point of view from which to approach the problem of post febrile cardiac irritability so often seen after influenza, trench fever, and occasionally after typhoid itself.

The subject matter of our study is so comprehensive and the phenomena which it comprises so complicated that it is necessary to define, in the first place, the limits of the field of disease to be dealt with, and in the second, the method of survey to be employed. The infectious and toxic processes of disease represent a large portion of the whole field of pathology. The circulatory system is the vehicle of nutrition for the whole organism, and in its functional activity it is delicately adjusted to the demands of the whole economy. The efficiency of its activity may be prejudiced by damage involving its structure or by poisons which depress or exhaust its vitality without producing gross or even microscopic lesions. On the other hand, it may fail in its accommodation by virtue of the mechanical burden it is called upon to bear, as, for example, in the bronchopneumonia of children with rickety chests and extensive atelectasis, where it is deprived of the normal accessory forces of the respiratory movements.

It is obvious then that an exhaustive treatment of the problem would carry us far beyond the object we have in view, that object being the presentation of the main features of the subject which are of practical importance to the practitioner, not only in recognizing pathological states and in providing a rational basis for treatment, but in stimulating his interest to further observation beyond the confines of our present knowledge. By "infectious and toxic processes" is meant here: (1) the acute infections, such as typhoid, typhus, scarlet, measles, whoopingcough, diphtheria, pneumonia, trench fever and the pyogenic infections; (2) the subacute infections or granulomata, syphilitic and tuberculous; and (3) those infectious or toxic processes, such as rheumatism, chorea, pernicious anemia and metallic poisoning in which reasonable doubt may be entertained as to the causal participation of organisms.

The method of survey will include: (1) a general review of the structural and functional disorders of the circulatory system which are characteristic of these infectious and toxic processes; and (2) a special review of the individual infectious and toxic processes in so far as their course is influenced by involvement of the organs of circulation.

The General Pathology of the Circulation in Infectious and Toxic Processes

Pathological anatomy is the groundwork of modern medicine. Other sciences make their indispensable contribution to the successful practice of the medical art, but the conception of a structural basis for disease is the fundamental principle to which every other consideration must be subordinate. In the classical work of the Hunters, of Rokitansky and of Virchow, the foundations of scientific medicine have been laid, and to overlook their work and its developments is to venture into an atmosphere of chaotic and futile speculation.

But the physician who expects from the pathological anatomist the explanation of all the complaints with which he has to deal is entertaining a vain hope. Only a limited number of complaints can be correlated with the conventional designations of pathological nomenclature, for complaints belong to the realm of mind, while diseases fall into the sphere of biology in its narrower sense. The problem is only partially relieved of its intricacy by setting aside the psychological element of the symptom or the peculiar individual coloring which each patient, in virtue of temperament or disposition, gives to his own account of his disability. There remains for consideration the fact that the organism may suffer in one or more of its systems from the transient effects of poisons which possess a special affinity for special structures without producing results which come within the purview of the anatomist. Alcohol, morphin, strychnin, muscarin, nicotin and pilocarpin may give rise to symptoms, derangements or disabilities, whose fleeting course leaves no trace of organic damage, and whose interpretation, even in the hands of physiologists or pharmacologists, is more or less a matter of opinion. The noxious substances elaborated directly and indirectly in the processes of mixed infection and intoxication are no less elusive in their mode of action. Even where substantial grounds exist for the tentative explanations of such toxic phenomena, there remain the reflex and mutual play of reactions between the various systems of the organism integrated by a nervous mechanism varying in its sensitiveness under both normal and abnormal conditions, and activated in its functions by internal secretions whose properties and conditions of production are obscure even in normal states, and whose behavior under abnormal conditions is even more obscure.

The Myocardium.—A clear conception of the structure of the cardiac musculature is essential to an understanding of its diseased states and their significance. Although it originates as a thickly meshed reticulum of mesenchymal cells with their bodies in regular contact with each other, the heart muscle is a syncytium whose striated fibrils run through the reticulum regardless of the so-called cell boundaries. These boundaries or intercalary discs are interposed in the course of the continuous fibrils which unite the cells into fibers; the fibers branch and their branches unite neighboring fibers into the syncytial structure of the finely transversely striated cardiac musculature. A very fine connective tissue surrounds the reticulum. The amount of the connective tissue increases normally with advancing years, and is always more prolific in the auricles than in the ventricles. The fibers of the ventricles possess a constancy in size and structure compared with those of the auricles, in which the fibers are usually thicker and more varied in appearance. Distinct in appearance, site and function is the specialized musculature of the heart, the sino-auricular and auriculo-ventricular systems which are concerned with the initiation and regulation of its coordinated contraction; this special muscle is poor in the development of its striation and is rich in glycogen. When stained with the van Gieson stain, it is paler than the contractile muscle, and its fibers are surrounded by a relatively large amount of connective tissue. The fibers show an intimate connection with nerve structures, and in the main course of the two systems, before they enter into intimate association with the ordinary musculature, they are separated from that musculature by layers of connective tissue. One system, the sino-auricular special muscle or node of Keith and Flack, is situated in the sino-auricular grove and in the region of this node the first demonstrable signs of cardiac contraction take place. The other system of special muscle, the auriculo-ventricular node and bundle is situated in the inter-auricular septum on the roof of the inter-ventricular septum just in front of the coronary sinus. This node is continued into the main auriculo-ventricular bundle which runs along the roof of the inter-ventricular septum till it reaches the septum fibrosum, where it divides into the right and left main branches and these branches run down on either side of the inter-ventricular septum beneath the endocardium and, separated from the ordinary musculature by fibrous tissue, their arborizations come into association with the contractile muscle as they approach the trabecular and papillary muscles of the ventricles. It is important to recognize the special site and function of these systems of coordinating musculature, inasmuch as certain degenerative processes in the heart depend not so much on the extent as on the location of the disease.

After the first year of life small masses of pigment appear at the poles of the muscle nuclei. These pigment granules stain with osmic acid and with Sudan III and may be mistaken for fat. They possess no pathological significance.

There are two subjects of controversy which may be disposed of here; Much has been written about segmentation and fragmentation of the cardiac muscle fibers; by segmentation being understood an interruption of the continuity of the fibers at the intercalary discs, and by fragmentation a discontinuity between the discs. The former is exceedingly rare and the latter is very frequent in advanced years, and does not occur in infants. the latter possesses no pathological significance; it is an agonal incident whose condition is probably related to the occurrence of the extreme contraction or distension of the organ at the time of death. The second subject of controversy has arisen from the conception of the heart as a parenchymatous organ like the kidneys or liver. Basing his observations on this conception, Albrecht and his followers have attempted to explain enlargements and weakness of the heart as being due to a compensatory effort to make good the defect due to chronic inflammation of the organ. But the heart is not a cellular organ in the same sense as the kidney or the liver. It is composed of muscle fibers united to each other by branching, and only such observations as are based on a recognition of this elementary fact require attention.

1. *Albuminous Degeneration.*—In all infectious and toxic states there is likely to occur albuminous degeneration or cloudy swelling of the muscle fibers which is difficult to distinguish from post-mortem degeneration. This consists in the deposit of albuminous granules between the fibrils, which disappear on the addition of dilute acetic acid. The muscle substance appears to the naked eye cloudy and less transparent than in the normal state. It has a somewhat dirty appearance and is flabby and easily torn. The kidneys and liver exhibit corresponding changes. Nothing is known of the clinical significance of these regressive metabolic processes except that they occur in febrile and toxic conditions.

2. *Fatty Degeneration.*—Fatty degeneration of the cardiac muscle shows itself microscopically either in the diffuse form of a yellowish muddy discoloration of the musculature or in a patchy form best seen on the endocardial surface, where it presents the characteristic thrush-breast appearance. Microscopically the fat droplets are arranged in rows between the muscle fibrils with larger droplets in the perinuclear sarcoplasm. It is not associated with gross destruction or disturbance of the muscle structure and is most marked in anemias, phosphorus poisoning, acute yellow atrophy of the liver, and in some conditions of chronic heart failure. Its clinical importance has been much overestimated in infectious and toxic states. It does not, at any rate, appear in a degree sufficient to exercise a determining influence on the course of events.

Fatty infiltration is quite distinct from fatty degeneration and consists in a proliferation of epicardial fat which, when excessive, infiltrates the spaces between the muscle bundles of the heart, especially in the region of the conus of the right ventricle. It occurs in persons showing other evidences of adiposity. It has no association with infectious or toxic processes, although it may exercise a baneful influence on the cardiac strength and render the heart more liable to premature exhaustion in toxic states. At any rate it has been held responsible for cardiac failure in chloroform narcosis.

3. *Vacuolar Degeneration.*—This form of degeneration occurs for the most part in cases of chronic valvular heart disease. It is more pronounced in the auricular than in the ventricular fibers. Both fatty and vacuolar degenerations are associated with edema and with defective circulation and oxygenation and are seen in the secretory cells of the kidney. It is of no importance in the present study.

4. *Waxy and Hyaline Degeneration.*—This consists in homogeneous clumping of the content of the muscle fiber, complete destruction of its structure, and the abolition of its function, and is the most important form of metabolic degeneration found in acute infectious and toxic processes; it occurs in diphtheria and typhoid fever and occasionally in pyemic infection, in which condition it is occasionally seen also in the somatic musculature.

5. *Necrosis.*—Necrosis occurs in the neighborhood of septic infections due to emboli in pyemic states. Its clinical significance for the heart depends upon its site and extent, but in the long run it is of course only one evidence of what is usually a fatal infection. Necrosis may occur also in infarctions due to emboli from non-pyogenic valvular vegetations or it may be due to a defective blood supply, from narrowing of the coronary arteries, a condition for which syphilis is for the most part responsible.

It has been deemed necessary to make the foregoing reservations and explanations in order to be able to define precisely the contribution which pathological anatomy can make to the solution of our problem. However important it may be to find in altered structure an explanation for a disordered function, that explanation loses its validity unless the limits within which it is applicable be accurately defined. It should be clearly understood that, while some circulatory disabilities in infectious and toxic processes can be correlated with structural alterations and disintegrations, there are others which cannot, and it is the business of the observer to discriminate, in the first place, which are and which are not, and in the second place, to extend as far as it is possible, the field of the known into that of the unknown. It remains now to consider separately the phenomena included under myocarditis; endocarditis; peripheral degenerations in the circulatory system in infectious and toxic processes; peripheral disturbances in the circulation in infectious and toxic processes; the effect on the circulation of extra-circulatory conditions incident to infectious and toxic processes; and, finally, the circulatory relations of certain infectious processes of particular importance in relation to the circulation, rheumatism, diphtheria, syphilis, and acute infectious endocarditis.

MYOCARDITIS

1. *Simple Acute Myocarditis*

The term "myocarditis" applies here exclusively to conditions in which the myocardium is the seat of inflammatory reaction. It is characterized by cellular infiltration and proliferation of the interstitial tissue accompanied, not infrequently, by degenerative processes of the substance of the muscle fibers, and in many cases, by the disappearance of the contractile elements (waxy degeneration). In some cases the reaction occurs in isolated masses, and in others it is diffuse. In most cases, it is most marked in the neighborhood of small vessels, and in others, it predominates in the interstitial tissue between the muscle bundles.

Mononuclear and polymorphonuclear leucocytes, and plasma cells appear in varying proportions in different cases. Variations in the size, shape and affinity of the muscle nuclei for alkaline dyes constitute a prominent feature, although such variations are seen also in hearts which exhibit patchy fibrosis due to defective coronary circulation. Enlargement of the nuclei is an evidence of retrograde change due to defective nutrition, and not, as has been suggested, the sign of compensatory hypertrophy. Interstitial infiltration may be quite independent of parenchymatous degeneration; perivascular, intramuscular and sub-endocardial inflammation may occur without any evidence of the retrograde metabolic changes which indicate destruction of muscle fibers. In diphtheria for example, one may find extensive inflammatory reaction without serious involvement of the contractile tissue, while diffuse waxy change may occur without interstitial reaction, to begin with at least. On the other hand, cases are seen in which the parenchymatous and connective tissue changes are both present in varying degree. Occasionally the perivascular and perineuritic infiltration constitutes a special feature of the anatomical picture.

The foregoing description applies more particularly to the forms of myocarditis seen in diphtheria and very occasionally in typhoid infection. In marked contrast with this, and easily distinguished from it is the lesion which is characteristic of the carditis of rheumatism and chorea. This latter consists in an interstitial and sub-endocardial distribution of submiliary nodules, whose outstanding feature is the radial or fan-shaped arrangement of connective tissue cells with large clear nuclei. The nodules are oval in shape, often surrounded by fibrin and in close association with perivascular tissue. Small areas of necrosis and giant cells may be found in the center of the nodule, which may be surrounded and infiltrated by other cellular elements of the nature of lymphocytes, granular leucocytes and plasma cells. The lesion of recent rheumatism of the heart cannot be distinguished from that of recent rheumatic fibrositis or myocarditis in the skeletal structures. It is in each case essentially an involvement of the connective tissue, although in many instances the adjacent muscle fibers may be affected. While the myocarditis of diphtheria and typhoid shows itself for the most part in the degeneration and destruction of contractile elements, the myocarditis of rheumatism is, for the most part, a fibrositis and shows itself in a typical infiltration of the tissue outside of the muscle bundles.

These two types of inflammatory reaction, as exemplified in diphtheria and typhoid on the one hand and in rheumatism on the other, may be observed also in skeletal muscle; the former being seen most frequently in the abdominal muscles in typhoid fever as waxy degeneration, and the latter in the acute fibrositis or fibromyositis of rheumatism in the somatic musculature, especially in the trapezius, lumbar, gluteal and pectoral muscles. It should be pointed out, however, that while the waxy degeneration of the abdominal muscles in typhoid is accompanied by interstitial reaction, there has not yet been described in these muscles a form of degeneration corresponding to the acute interstitial and intramuscular myocarditis of diphtheria with its diffuse destruction of contractile substance.

Arising from specific and contributory causes and exhibiting each a distinct structural reaction, these forms of myocarditis may be compared in the course which they run and in the effects which they ultimately exercise on the heart. The diphtheritic type, if it does not lead to death, progresses within a few weeks to a final fibrosis of the affected areas. The waxy fibers become absorbed and are replaced by cicatrices. Other fibers, which have been partially digested in the inflammatory reaction, are absorbed in the process of healing and the interstitial granulations contract and harden into fine connective tissue bands. Once cicatrization has been completed, a final stage in the process of healing has been reached, unless of course, in the unlikely event of reinfection. The liability to subsequent cardiac failure depends exclusively on the initial damage to the heart and on the advent of new features outside of the range of the diphtheritic infection. The original damage, however, may have been so great as to lead to permanent disability, which may show itself in the ready exhaustion of the patient, slight dilatation of the heart with mitral incompetence and occasional irregularity of its action. The reserve force of the organ may be so diminished as to render impossible the exertion and activity of a normal physiological life and, although the disease is not progressive in a histological sense, the original damage may be a determining factor in the production of cardiac failure in the course of a subsequent infection of another kind.

In the case of rheumatic myocarditis, the muscle fiber is not so seriously affected and the immediate danger is not so great, but the period of recovery is more uncertain. With the passing of the acute phase the nodules and interstitial granules become fibrosed. In the case of diphtheria, one may be fairly certain that in three or four months from the onset of infection the progress of the disease has been arrested, while in the case of rheumatism there is constant liability to recurrence. Endocardial rheumatism may have occurred, although in recent cases the signs of these are equivocal. A mitra systolic murmur may be the evidence of dilatation only, but it may also be the indication of an organic lesion constituting the original focus of later developments. So tenacious is the poison of rheumatism that, once having found a seat in the heart, the probability is that it will recur, if not in one form, at least in another.

2. *Acute Septic Myocarditis*

This condition arises as a complication of septicemia or pyemia, and may or may not be associated with ulcerative endocarditis. When it is due to showers of minute emboli, there are multiple abscesses of microscopic dimension; when it is associated with ulcerative endocarditis there may be larger and isolated emboli in the coronary arteries, producing abscesses of considerable size which may break into the cardiac chambers or even produce rupture of the heart wall. The cardiac signs are of course overshadowed by the other evidences of pyemia, and the prognosis is always grave.

3. *Acute Idiopathic Myocarditis*

This is a form of acute interstitial myocarditis of unknown origin. It runs a rapid and usually a fatal course. It presents the signs and symptoms of a general infection, and on post-mortem examination the only gross evidence of disease is in the myocardium. There is a patchy necrosis of muscle with diffuse interstitial infiltration. The histological picture resembles in many states that of an acute rheumatic myocarditis, although in a more extensive and intensive form than that observed in acute rheumatism. The cases are usually fatal.

4. *Syphilitic Myocarditis*

Diffuse interstitial fibrosis of the myocardium is not uncommon in congenital syphilis. It is comparable with the fibrosis which is seen in other highly developed organs in that condition.

In acquired syphilis lesions of the myocardium are rare in comparison with the frequency of infection. Such lesions may take the form of isolated gummata or of interstitial fibrosis chiefly in the perivascular areas. Occasionally the specialized conducting system of muscle, auriculo-ventricular node and bundle, may be involved in a lesion spreading from a syphilitic aortitis and giving rise to the well known clinical phenomena of heart-block. The most serious disability to which the myocardium is exposed in syphilis is that due to lack of nutrition from the narrowing of the coronary arteries in the proliferative reaction of aortitis. The gross evidence of this may be seen in the patchy fibrosis which represents areas of anemic infarction. Such areas are not in themselves so much a source of myocardial weakness as an evidence of the impoverished state of the organ as a whole.

5. *The Myocardium in Tuberculosis*

Apart from the miliary nodules which occur in acute miliary tuberculosis, tuberculosis of the myocardium is exceedingly rare. Very occasionally caseous nodules have been observed and a tuberculous process may spread from the pericardium to the outer surfaces of the cardiac muscle. Tuberculosis of the myocardium has no clinical importance.

6. *Chronic Myocarditis*

This term is frequently employed without any underlying conception as to its precise meaning. There is no such disease as chronic myocarditis comparable with chronic nephritis or with cirrhosis of the liver or with the chronic syphilitic cerebritis of general paralysis of the insane. If the designation be applied to rheumatism or syphilis of the heart, then that should be done on the clear understanding that one or other of these diseases is present. Fibrosis of the cardiac muscle may, as has been pointed out, result from the poverty of the coronary circulation, or it may be the result of a diphtheritic typhoid, rheumatic or syphilitic lesion which has spent itself; but, in any case, the term is a general one and has no relation to any specific process outside of the various inflammations which have already been discussed.

7. *The Myocardium in Acute Infection*

The myocardium in pneumonia, scarlet fever, measles, smallpox, typhus and gonorrhea may possibly be affected by toxic agencies, but there is no anatomical evidence to show that myocarditis in the sense in which the term should be implied occurs in these diseases. In the febrile period the circulation is disturbed. The heart's action may be rapid or abnormally slow or even irregular; the cardiac chambers may be dilated and there may be mitral incompetence. The sounds may be impure and soft, but the probability is that these abnormalities are the transient effects of the toxins of the infection, not only on the heart itself but on the regulatory system of the circulation as a whole, and not due to any structural alteration of the myocardium comparable with the lesions which are characteristic of myocarditis as described above.

ENDOCARDITIS

For practical purposes the term "endocarditis" is applied to inflammatory states of the valvular endocardium although the process may occasionally spread to the mural endocardium and to the chordae tendineae. For descriptive purposes it is convenient to consider the subject under the arbitrary divisions:

1. Simple verrucose endocarditis
2. Acute ulcerative endocarditis
3. Subacute ulcerative endocarditis, and
4. Chronic endocarditis.

1. *Simple Verrucose Endocarditis*

This consists primarily in necrosis of the endothelium of the valves confined to those areas or parts of the areas of the valves which come into contact on closure. On the basis of this limited necrotic softening small excresences of fibrin are deposited from the blood. Blood platelets, white and red corpuscles and fibrin, constitute the composition of the row of minute transparent grayish white granules which form a narrow ring around the surfaces of contact of opposing valves. Microbes circulating in the blood are not infrequently deposited on the surface of these thrombotic masses, but these organisms, judging from their superficial position, have no causal relationship to the condition. This simple form of endocarditis is found in the last stages of the cachexia of ulcerating tumors, chronic nephritis, general tuberculosis and other wasting diseases in which the metabolism of the organism is perverted and its resistance low. It is an occasional post-mortem feature in pneumonia and enteric fever, where it probably originates in the moribund state.

Indistinguishable from this in its original appearance, but totally different in its significance in regard to possible developments, is the initial stage of rheumatic endocarditis. This condition begins, as described above, in the form of grayish white granules on the surfaces of contact of the closed valves, most frequently on the mitral, sometimes on the aortic, seldom on the tricuspid and practically never on the pulmonary valves. In some cases there may be a sand-like dispersal of the granules on the chordae tendineae or on the pars membranacea. In the early stages they are easily rubbed off. Gradually the valve structures in the neighborhood of the deposit show a reaction in the form of increase and enlargement of the connective tissue cells. The granules become firmer and less easily dislodged. Continuation of the process may lead to a confluent attachment of the adjacent corners of the valves to each other and to adhesions between adjacent chordae tendineae; the valvular tissue is not vascularized and in the early stage there is no true inflammatory reaction. If at this stage the process becomes spent the granules may become hyaline or calcified and the disease may pass off, leaving the valves damaged but slightly in the anatomical sense, and functionally unimpaired. But the virus of rheumatism is pertinacious in its attachment to the tissue in which it has once gained a seat. There may be a remission in its activity, but it is apt to reassert itself. A recurrence is accompanied by a renewal of valvular deposits, more extensive disintegration of the valvular structure and perhaps by a true inflammatory reaction on the part of the blood vessels at the base of the valves. Should this latter contingency arise, a process of vascularization of the valves produces an ultimate organization of the thrombi. Once this stage has been reached, the fate and ultimate efficiency of the valvular apparatus is compromised. Granulation is followed by cicatrization and its attendant consequences. In the case of the mitral valve, the cusps become hard and thickened; the chordae tendineae become shortened and the adjacent cords may granulate into a coherent mass. Progressive cicatrization is attended by increasing deformity of the valvular mechanism, the orifice becomes narrowed, auriculo-ventricular flow is impeded and the shortened chordae tendineae and thickening of the cusps render effective closure impossible during ventricular systole. In the case of the aorta, the free edges of the cusps become thickened, rolled in and retracted and valvular competence during ventricular diastole is rendered defective. Such mechanical defects are, however, made good to a large extent by compensatory hypertrophy of the cardiac musculature. The extent to which this is possible depends upon the degree of valvular defect and upon the condition of the muscle itself. Even a normal cardiac muscle, like other muscles of the body, has only a limited capacity to meet abnormal demands, and in the case of rheumatism, as has been noted above, the musculature is not infrequently itself the seat of pathological reaction. This holds good in spite of the fact that the main evidence of the activity of the rheumatic poisoning is found, not in the protoplasm of the muscle fiber, but in the interstitial and sub-endocardial layers which, though not contractile, contain elements which are no less important to the normal activity of the cardiac action. Prejudiced by valvular incompetence drawing disproportionately on the reserve strength of a diseased or even healthy contractile mechanism, and constantly exposed to the possibility of a recurrent poisoning, it is not difficult to imagine the precarious state and limited possibilities of the subject of rheumatic endocarditis. If, on the easy routine of life there be imposed undue physical or mental exertion or the burden of pregnancy, it is easy to imagine the premature exhaustion of the limited amount of reserve. On the other hand the course of the disease may be interrupted and the disability aggravated by incidental pericarditis, pleurisy with effusion, nephritis or pulmonary or brain embolism.

Progressive constriction of the mitral orifice may lead to hypertrophy of the auricular muscle with subsequent muscular degeneration, and such degeneration may be accompanied by paralysis of the auricular function with its well known clinical signs. Further discussion of this aspect of the question does not belong to our subject.

2. *Acute Ulcerative Endocarditis*

This form of endocarditis is due to pyogenic infection of the valves. In its early stages and especially in acute and fatal septicemias it presents appearances which are not readily distinguished from those of simple verrucose endocarditis described above. Depending upon the virulence of the infection and upon the length of time in which it is in process, the changes in the valves may vary from a condition in which there is merely a narrow row of granular deposits on the edges of contact during closure, to a condition in which the apertures are partially closed by the growth of large fungoid or polypoid thrombi. In rapidly progressing septicemias small opaque granules of a dirty yellow color are deposited on the auricular surfaces of the mitral or on the ventricular surfaces of the aortic valves. As a rule they are more irregular than the corresponding excrescences seen in the simple verrucose type; and in the region of the lesion the valve presents a dry and raw-looking appearance. A smear preparation from the lesion shows large numbers of micro-organisms. Should the process be prolonged, large thrombi develop on the bases of these initial lesions. The ulcerative process may extend onto the cardiac walls. The valves may be perforated; the aorta may be invaded with destruction of its wall causing the formation of aneurysm or rupture. The thrombi on the aortic valves may be so large as to produce a partial or complete occlusion of a coronary artery. The chordae tendineae may be severed and float freely in the ventricular cavity, and even portions of the mitral valve may be separated from the main structure. The main stem of the auriculo-ventricular bundle may be invaded by an extension of the process either from the aortic or from the mitral valve, thus giving rise to an interruption of the auriculo-ventricular rhythm. Interference with the valvular competence by the extension of the ulcerative processes may lead to rapid failure of the heart from mechanical causes.

The more remote effects of the condition depend upon the character of the local reaction and especially upon the consistence of the thrombotic masses. If the masses are soft, necrotic and fragile, then a dispersal of emboli laden with pyogenic microbes gives rise to miliary abscesses all over the body. The symptoms of the spread will depend upon the location of these secondary infections. In the unlikely event of a subsidence of the acute valvular infection the resulting process of healing and cicatrization will leave a deformity and deficiency of the valvular apparatus more severe than that seen in the usual forms of chronic encodarditis.

3. *Subacute Ulcerative Endocarditis*

Infective endocarditis may run a chronic course. In that event it is usually due to a pyogenic infection imposed upon an old valvular defect. The anatomical changes consist in indolent ulceration of the affected valves and spread of the process into the adjacent structures. The micro-organisms are situated deep in the base of the ulceration and there is practically no tendency to the production of thrombotic masses which are characteristic of the more acute kind. These cases may go on for months with anemia, weakness and obscure fever giving rise to an extremely puzzling clinical problem. This aspect of the question is dealt with later on.

4. *Chronic Endocarditis*

The chronic endocarditis of rheumatism and the subacute or chronic form of infective endocarditis have been discussed elsewhere. The only other form of chronic endocarditis of infective or toxic origin remaining for discussion is that due to syphilis. Syphilitic endocarditis arises in association with syphilitic aortitis, and this is fully discussed later on.

PERIPHERAL DEGENERATIONS IN THE CIRCULATORY SYSTEM IN INFECTIOUS AND TOXIC PROCESSES

While the arborizations of the cardiovascular system participate in the functional disorders which constitute the circulatory reactions to infectious and toxic processes, there is no evidence to show, except in the case of syphilis, that the vessels themselves are the seat of organic changes. In most febrile states the vasomotor tonus is relaxed, and the character of the pulse wave assumes the well known dicrotic quality. Attempts have been made to correlate the incidence of acute infections with the later development of arteriosclerosis. Fatty changes in the intimal endothelium have been regarded as a prelude to later sclerosis. It may be said with confidence, however, that much evidence is still required to establish the validity of this thesis. In the case of diphtheria and of rheumatism attention has been called to the fact that the inflammatory reaction in the myocarditis of these diseases finds its seat of preference not infrequently in perivascular areas. It can scarcely, however, be maintained that adventitial changes such as do occur in these conditions are the source of disturbances which are prejudicial to the course of the disease.

It sometimes happens, however, that involvement of vessels does occur as an incident in the infectious process. In ulcerative endocarditis, for example, the media of the aorta may become the seat of purulent infiltration, giving rise to aneurysm and even to rupture. Septic emboli from an ulcerative endocarditis may find their way into cerebral arteries and there give rise to aneurysm and hemorrhage. Local pyogenic infections may lead to septic thrombosis of neighboring veins, and the dislodgement of septic thrombi may be the determining incident in the development of pyemia. Complications of this character are not infrequently met with in mastoid disease and in puerperal sepsis. Very occasionally the ulcerative angina of scarlet fever may eat its way into the large vessels of the neck and give rise to fatal hemorrhage. But when these accidental complications are excluded, it may be said that the ordinary acute infections run their course, fatally or otherwise, without involvement of the extra-cardiac part of the circulatory system.

Tuberculous disease, to which no tissue of the body is immune, occasionally finds the seat of reaction in blood vessels. This does not occur, however, in the same way or to the same extent as in syphilis. It may be said that in tuberculosis the vascular lesion is accidental and its more serious complications extremely rare. In tuberculous meningitis there are infiltrations of the adventitia and media, and frequently also endarteritis. In this respect tuberculous meningitis bears some resemblance to syphilitic meningitis. The most serious tuberculous complications in the vascular system are, however, those in which the veins are invaded by a spread from disease in neighboring lymphatics. In a considerable proportion of cases, acute miliary tuberculosis is due to the formation of tuberculous thrombi on the intima of veins which are invaded from neighboring tuberculous bronchial glands; and occasionally the miliary spread may be found to originate in a similar invasion of the thoracic duct. A vascular incident which sometimes occurs in tuberculosis is the rupture of an aneurysm in a tuberculous cavity, the aneurysm originating from the erosion of the vessel wall by the ulcerative process.

The importance of syphilis in lesions of blood vessels is considered fully at a later stage. (p. 326)

Peripheral Disturbances in the Circulation in Infectious and Toxic Processes

Reference has already been made to the misleading tendency to look upon the heart as the sole organ of circulation and to forget altogether, or to regard as negligible, the part played by its arborizations in the maintenance of nutrition. In the evolutionary process the heart has undergone morphological and histological differentiation which enables it to propel the proportionately larger quantities of blood which are demanded by the tissues of animals whose life and metabolism have become more active. But such developmental adaptation is not confined to the heart; the blood vessels, arteries and veins exhibit a progressive differentiation in structure which may be taken to imply an increased capacity to meet the needs of a more varied and more strenuous existence. Even in the development from the horizontal to the upright posture, some regulatory adaption of the peripheral circulation must have occurred to avoid a disproportionate distribution of blood. To what extent the peripheral circulation is propulsive and to what extent it is merely regulatory in its distributive function can only be surmised. In health the whole system works so smoothly, its organic elasticity is so accommodating that the intricacy of the nervous and chemical factors by which it is integrated cannot be comprehended. There are incidents in infectious and toxic processes, however, which are not explained by degeneration or exhaustion of the cardiac muscle, or by interference with the intracardiac regulatory mechanism.

A girl of ten years, convalescing from diphtheria a month from the onset of signs of infection, suddenly becomes extremely pallid and restless. Apart from occasional irregularity of the pulse which has been noticed for two days no premonitory signs are observed. The pallor and restlessness remain, the pulse becomes rapid and there is occasional vomiting. There is tenderness over the liver and albuminuria appears. Without dyspnea or cyanosis or edema, death occurs a week after the onset of the complication On post-mortem examination an interstitial myocarditis is found; the inflammatory reaction predominates in the spaces between muscle bundles and around the muscles; there is only slight degeneration and destruction of muscle fiber. There is great congestion of abdominal viscera, especially of the liver. This must be a common experience to those who have had fever hospital experience. The clinical type may of course vary greatly; the patient may die suddenly without having previously shown evidence suggestive of cardiac weakness; on the other hand, the illness may be prolonged over several weeks, with periods of pallor, restlessness, in some cases apathy, and sickness alternating with periods of comparative well-being, and in the end the patient dies, or very occasionally recovers.

This condition is not confined to diphtheria. We have seen it on three occasions in rheumatism. A girl, twelve years of age, in the fifth week of convalescence from rheumatic fever, exhibited a sudden change in the course of recovery. The high temperature of the initial fever had subsided in three days, but there was an occasional rise from time to time up till the onset of the complication referred to. The heart was slightly dilated to the left, a mitral systolic murmur was present and myocarditis was suspected. The main features of the new development were extreme pallor, sudden rise in rate of pulse from 90 to 120 per minute with fall in the pulse tension, and extreme restlessness; she complained of pain over the heart; there was no dyspnea, no cyanosis and no sign of pulmonary congestion; the pallor and restlessness continued, albumin appeared in the urine and there was tenderness on pressure over the liver. There was occasional sickness. The picture was typical of that seen in diphtheria, so much so that, in spite of the rheumatic fever, diphtheria was suspected. She died on the fifth day of the complication, and post-mortem examination revealed the characteristic lesion of rheumatic myocarditis. The nodular infiltration was most extensive around the vessels in the fibrous septa between the muscles and in the sub-endothelial tissue of the left ventricle. There was a recent endocarditis of the mitral cusps. But this had no importance from the point of view of mechanical efficiency. The heart was flaccid and dilated, and there was intense vascular enlargement of the abdominal viscera.

There occurred in each of these cases a well defined series of clinical phenomena which commenced unexpectedly in the course of the disease: sudden pallor, restlessness, and sickness; rise of pulse rate with albuminuria and enlargement of the liver, but without dyspnea, cyanosis or edema. These are not the signs of cardiac failure in the strict sense in which the term is employed clinically. They are the signs of shock; and the post-mortem evidence pointed conclusively to the draining of the blood into the splanchnic circulation, with the consequent superficial pallor, anemia of the brain and insufficient supply of blood to the heart to stimulate the normal rate of contraction. Call it shock, call it what one may, the condition is essentially the same as that which sometimes follows a severe wound, or that which follows dilatation of the sphincter in the operation for hemorrhoids, or that which occurs occasionally during the excision of a tuberculous knee-joint, or during operation for circumcision. It is suggested that stimuli passing from the diseased heart so influence the vasomotor control as to produce the determination of an unduly large proportion of the blood to the abdominal vessels and viscera. It may be objected that this is an extremely rare occurrence; but so is acute myocarditis apart from diphtheria and rheumatism, and the peripheral disturbances described are by no means an infrequent complication of diphtheria. It is probably also the most frequent complication in those cases of acute rheumatism where the patients die early and unexpectedly in the course of the disease. Whether and to what extent, and in what manner, the peripheral circulation is disturbed by, or adapted to, or compensated for, in chronic disorders of the heart are not problems which concern us here; that they are problems of first rate importance cannot be denied.

The Effect on the Circulation of Extra-Circulatory Conditions Incident to Infectious and Toxic Processes

The maintenance of an effective circulation depends not only on the normal structure and activity of the circulatory apparatus itself, but also on the effective cooperation of accessory forces which assist in the propulsion of blood. Chief among these is the mechanism of the respiratory movements, and any infection or disease which compromises the freedom of respiratory movements throws an embarrassment on the circulation. In acute lobar pneumonia, for example, it is extremely difficult to estimate the importance of the various factors which contribute to a fatal issue.

The infected patient is subjected to the adverse influences of a complicated series of abnormal processes, which, for the sake of convenience, may be termed chemical and mechanical. The chemical agencies, in addition to oxanemia, include the disintegrating bacteria, the local products of the reaction between the micro-organisms and the host, and various other substances of abnormal quantity or quality which originate as a result of the interference of toxins with the normal metabolism in parenchymatous organs. These processes manifest themselves in well recognized anatomical changes in the liver, the kidneys and the cardiac muscle, and the clinical manifestations of the disease indicate a reaction on the part of the nervous system also. The degree to which the parenchymatous organs are affected depends on the amount of abnormal chemical substances present, and the affinity of these for the affected organs. The progress of the disease will be determined largely by the reaction of the bone marrow and other tissues which supply the anti-substances necessary to hold the noxious chemical processes in check. The issue of pneumonia, however, may be influenced by the mechanical conditions incident to the disease. The pain of the pleurisy interferes with free movement of the chest wall, and an extensive consolidation, too, limits the expansion of the thoracic cavity and creates an obstruction to the pulmonary circulation; the work of the right ventricle is thus increased, and the efficiency of the organ may be seriously prejudiced.

However, it is in the case of those conditions which are classed collectively as bronchopneumonia in children that mechanical difficulties are most pronounced. Rapid respiration and cyanosis are common features of bronchitic affections, more especially when accompanied by rickets and atelectasis. In many of the cases the toxic effects of the pneumonia are much less serious than the physical disability under which the heart suffers in maintaining the circulation. An extensive clinical and correlated post-mortem experience has established this fact beyond all doubt.

Within very narrow limits the healthy heart preserves a definite shape and size, varying only with the weight and age of the individual. There occur, however, in certain pathological conditions well recognized modifications of shape and size. In chronic Bright's disease the left ventricle becomes greatly enlarged. The nature of this enlargement and change of shape is fairly constant and gives an abnormal shape to the pathological heart. Aortic and mitral disease are also responsible for enlargement and change of shape more or less characteristic of these diseases; the heart of aortic regurgitation, for instance, is known as the "cor bovis." Where there is tuberculous adhesive pleurisy or chronic fibrotic phthisis the right side of the heart is often enlarged and a similar variation is not infrequent with chronic bronchitis and emphysema. Now, with the exception of the latter cases, the cardiac change is associated with an interference with the normal dynamic conditions inside the vascular system itself. On the one hand the peripheral blood pressure is increased by the vaso-constriction of chronic Bright's disease, or by changes in structure of the smaller vessels in arteriosclerosis; or, on the other hand, the mechanical efficiency of the pumping apparatus is compromised by the valvular defects in the cardiac apparatus itself, and the enlargement is the result of an attempt to compensate for this defect. When, however, a change in the size and shape of the heart is observed in an otherwise normal vascular system, associated with advanced disease of the lung or chest wall, one has then to deal with the result of extraneous influences, with the effect on the vascular apparatus of forces from without, and the extent to which an interference with normal pulmonary expansion can be correlated with increase in the size of the heart may be taken as indirect evidence of the part played by the normal respiratory movements as factors which make for an efficient circulation.

The circulatory burden of respiratory difficulty is most frequently observed in: (1) extensive collapse of the pulmonary tissue (atelectasis); and (2) in rachitic or tuberculous deformity of the thoracic cavity.

(1) *Cases Illustrative of Atelectasis and Cardiac Failure*

Case 1.—A girl of seven and a half years, fairly well developed, had a severe diphtheria followed by paralysis of the muscles of deglutition. An aspiration pneumonia was supposed to have followed, and after eight weeks' illness she died. For a fortnight previous to her death she was very pale and suffered from breathlessness, and for some days before death there was edema of the lower limbs. Post-mortem examination showed very extensive atelectasis in both lungs, the right upper lobe and the left lower lobe being completely collapsed; while the remaining lobes were greatly distended. The child weighed 3 stone (42 lb. or 19 kilos.), and the heart weighed 7½ oz. (212.6 gm). The form of the heart was abnormal. It was broad proportionately at the base of the ventricles and rounded or almost flattened at the apex, and both ventricular walls were hypertrophied. The venous system was engorged, and the parenchymatous organs showed signs of passive venous congestion. The cardiac muscle showed no signs of fatty or fibrotic degeneration.

Case 2.—A boy of two years was admitted to the hospital suffering from bronchopneumonia. He died after an illness prolonged over ten weeks. He was fairly well-developed and the chest was of normal shape. During the last two months of illness he was pale and his respirations were rarely under 50 per minute, and sometimes were 80 per minute. The pulse ranged between 140 and 160 per minute. While at the beginning of his disease the temperature varied between 101° and 103.6° F, for a period of a fortnight during the last six weeks there was no febrile disturbance beyond an occasional rise of temperature to 101° and 102° F. For a few days before death there was edema of the lower limbs. Post-mortem examination in this case showed the heart to be enlarged and relatively broad over the whole extent of the ventricles. The interventricular septum, as demarcated by the descending coronary artery, occupied a relatively normal position. The heart weighed 4 oz. (113.4 gm.), and the body weighed 22 lb. (9.9 kilos.). On opening the heart, both the ventricles were found to be hypertrophied. The shape of the heart was abnormal with great hypertrophy of the walls, more especially of the right ventricles and the septum. On microscopic examination the cardiac muscle showed no signs of fatty or fibrotic degeneration. The lungs were collapsed along their posterior portions and at places along the anterior margins. Microscopical examination showed that the pathological lesion was one of collapse. While the evidence of old bronchopneumonia was still present, the process was no longer an acute one, and there was no sign of recent inflammation. There was great engorgement of the whole venous system, and passive congestion of the parenchymatous organs.

(2) *Cases Illustrative of Chest Deformity and Cardiac Failure*

Case 1.—A girl, eight years of age, with very extensive rickety deformity of the chest and lower limbs, was admitted to the hospital on account of breathlessness. While under observation, extending over five weeks, she had no abnormal rise of temperature. The chest movements were described as being restricted in the upper part of the thorax. The respirations numbered 30 to 50 per minute, and the pulse from 130 to 150 per minute. Post-mortem examination showed that the heart weighed 7½ oz. (212.6 grams), while the body weighed 30 lb. (13.6 kilos.). The heart was of firm consistence, relatively broad, and with a somewhat rounded broad apex and short in length from the apex to the base of the ventricles. On opening, it was seen that both ventricles had participated in the hypertrophy, although the most marked hypertrophy was that of the interventricular septum. The right auricle was dilated. The cardiac muscle showed no signs of fibrotic or fatty degeneration. The lungs were greatly distorted in shape. The anterior margins were collapsed, and a line of depression was present on the anterior surfaces corresponding to the site of junction of the ribs with the costal cartilages. The distortion of the lungs at this line of depression was so great as to give the anterior borders the appearance of being tilted forward about 45 degrees from their normal position. The anterior borders were airless, and there was considerable collapse on the posterior aspects of the upper lobes of both lungs. There was no evidence of acute inflammation in the lungs. Examination of the thoracic cavity showed a striking deviation from the normal. It was greatly contracted in its upper half, and this contraction was due to an in-sinking of the ribs along the line of their junction with the costal cartilages. It was as if pressure had been exercised along this line on either side, in a direction downwards and inwards so as to produce an approximation towards the middle line, and an obliteration of the upper and anterior part of the thoracic cavity. Towards the diaphragm the cavity widened, and the line of depression gradually disappeared. The ribs were firm and well ossified. There was general venous engorgement and passive congestion of the parenchymatous organs.

Case 2.—A boy of one and one-half years had an extreme rickety deformity of the chest. The chest was of the fiddle-shaped type, very much contracted at the level of the axilla, and expanded at the insertion of the diaphragm. Respirations were rapid and shallow, varying from 50 to 80 per minute, and the pulse rate was from 150 to 180 per minute. The respiratory movements were confined almost entirely to the abdomen and lower part of the thorax. For a week before death there was edema of the lower limbs. Post-mortem examination of this case showed an abnormal size and shape of the heart. The organ was of firm consistence. It was broad at the base and relatively short from the apex to the base of the ventricles. The apex was rounded off in the arc of a very large circle. The anterior interventricular groove was not displaced relatively. The right auricle was greatly distended. A transverse section through the ventricles showed marked hypertrophy of the walls of both chambers, more especially perhaps of the right ventricular wall and the interventricular septum. The shape and degree of the hypertrophy of the heart resembled almost exactly the condition seen in Case 2 under atelectasis, where there was extreme collapse following a bronchopneumonia, but no deformity of the chest wall. In this case the heart weighed 3½ oz. (99.2 grams), and the body weight of the child was 21 lb. (9.5 kilos.). There was no fatty degeneration or fibrosis of the cardiac musculature. The lungs were distorted, the anterior portion being marked off by a deep furrow which corresponded in site with the line of junction of ribs with costal cartilages. There was a considerable degree of collapse along the anterior margins in front of the furrows, and there was also extensive atelectasis in the posterior portions of both lungs, more especially in the upper lobes. There was no evidence of recent inflammation. The thoracic cavity was very much diminished in extent. The only portions which retained their normal contour were the recesses on each side of the vertebral column posteriorly. The anterior mediastinum was almost obliterated by the in-sinking of the ribs along the line of the rosary. The thoracic cavity was enlarged on the plane of the diaphragmatic attachment. The ribs were soft and pliable, and could be bent like green wands. They contained practically no true bone substance. It was possible to cut microscopical sections of some parts of the ribs without subjecting them to a process of decalcification. The venous system was congested, and there was passive congestion of the parenchymatous organs.

On reviewing the results of these observations, *i.e.*, the four cases just described, one common characteristic emerges; in each case the heart is about double the normal weight relative to the weight of the body, and in each case the enlargement is unassociated with any other abnormality of an anatomical nature in the vascular system. As regards the hypertrophy itself, it is to be noted that while the right side and interventricular septum participate in a greater degree, there is also in every case hypertrophy of the left ventricle. The associated anatomical abnormality is in every case that of a part of the respiratory mechanism, the lungs, the chest wall, or both. The facts, then, which present themselves for correlation are these:

1. General hypertrophy of the heart in an otherwise normal vascular system, with relatively greater increase in size of the right side, ending in cardiac failure.
2. Collapse of the pulmonary tissue and deformity of the chest wall.

The heart of the healthy subject maintains a size which bears a definite relation to the size and weight of the individual, and which is independent of the amount of bodily exertion within very wide limits. The heart of a man who pursues a sedentary occupation, is no smaller than that of a man whose occupation involves a moderate amount of physical exertion, and the amount of work performed by the organ may be greatly increased without in any way prejudicing its efficiency or increasing its size relative to the weight of the body. This property of adaptability is inherent in the heart and is aided by compensatory variations in pressure throughout the vascular system regulated by the vasomotor apparatus. The increase in size of skeletal musculature, resulting from physical exercise, develops, *pari passu*, with an increase in the weight of the heart, and the extra work entailed on the left ventricle is balanced by the aid afforded by greater muscular activity in returning the blood through the venous system. The increased thoracic movements in additional muscular activity contribute also to meet the extra demand which is put upon the circulatory apparatus. Moreover, the cardiac muscle itself would seem to possess the capacity of immediately adapting itself to an emergency; for example Stolnikow has shown that, when a ventricle in diastole is artificially filled so as to contain even six times the normal amount of fluid, it is able with the next systole to drive out several times the normal amount; and in the same way an increased arterial resistance is immediately overcome by the succeeding ventricular contraction. The heart thus possesses an enormous power of adaptation, and when it shows signs of great hypertrophy and consequent inefficiency such a condition may be regarded as being due to one or more of the following causes:

1. Increased work determined either by an increase in the number of beats per minute, as in exophthalmic goiter, or by increased force demanded against abnormal peripheral resistance, as in renal disease or arteriosclerosis.
2. Some defect in the pumping apparatus itself, such as stenosis of the valvular orifice or valvular defect causing regurgitation.
3. Failure of accessory powers of circulation, which include the variations in intrathoracic pressure, the expanding and collapsing lungs, and the movements of the skeletal muscles.

When the cases described are viewed in the light of these considerations, it is obvious that the causes referred to under the third heading constitute the main factors in the production of the cardiac enlargement; at the same time it must be recognized that in each case the pulse rarely was abnormally high although even here the increased pulse-rate was probably secondary to the increased respiratory-rate, or associated with the cyanosis incident to the deficient respiration. In any case, the factors that are anatomically associated with the hypertrophy are: (1) atelectasis; (2) rachitic softening with distortion of the thoracic wall.

Atelectasis and Cardiac Failure

In the present state of knowledge it is impossible to determine exactly the modification of physiological respiration which is determined by collapse of a considerable portion of the lung. Possibly a vasomotor reaction plays a part, accommodating the organism to the new conditions, or, reflex contractions of the muscular rings of the bronchioles may exercise a regulating influence on the disturbed balance of pressure. The physical changes are those, however, which are most easily estimated. When a portion of lung collapses, there occurs with inspiration distention of the alveoli of the expanding parts; at the same time the relatively diminished pressure in the atelectatic portions determines a flow of blood to these parts, whereas the compensatory emphysema gives rise to a resistance to the blood flow through the distended portions of the lungs. In this way there occurs circulation of a considerable portion of blood through portions of lungs where oxygenation cannot take place, whereas the air circulates through portions where the emphysematous distention of the alveoli hinders the passage of the blood through the capillaries. The results of such a condition are:

1. Deficient oxygenation of blood, with dyspnea and increased cardiac action.
2. Increased resistance to the flow of blood through the emphysematous portions of the lungs, and the consequent embargo on the right ventricle.
3. Stagnation of blood in the collapsed portions of lung, with the result that the work of the right ventricle is increased, and in addition the heart is deprived of the assistance of the expanding and collapsing lung in furthering the blood flow.

Disease of the Chest Wall in Relation to Cardiac Failure

The diseases of the chest wall which are here concerned are:

1. Softening of the ribs due to rickets.
2. Deformities due to rickets, tuberculous caries, etc.

It is obvious that, where rachitic decalcification has produced softening of the bones, deformity is also certain to supervene. Such processes are most severe between the ages of nine months and two years. As a result of loss of elasticity and subsequent deformity, collapse of the lung tissue is not infrequent, so that the rachitic chest is further embarrassed by the conditions which have been considered in the preceding paragraph.

The nature of rachitic deformity and the extent and distribution of a concomitant atelectasis are worthy of notice because they afford a strong confirmation of the conclusion to which Keith has come regarding the mechanism of respiration in man. (See also Hoover, Respiratory Excursion of the Lung, Vol. II, Chap. II.) In emphasizing the necessity of recognizing surfaces of direct and of indirect expansion on the lung, Keith has rendered a great service to the study of pulmonary diseases in children. He has pointed out that the mammalian lung is not equally distensible in all its parts, and that it does not expand equally in all directions during inspiration. Of the five areas, he says, which one may distinguish on the surface of the human lung, three are in contact with stationary parts of the thoracic wall, and therefore cannot be directly expanded. These three pulmonary surfaces are:

1. The mediastinal in contact with the pericardium and mediastinal structures.
2. The dorsal surface lying between the spinal column and the spinal segments of the ribs; those parts of the ribs to which the erector spinae muscle is attached.
3. The apical surface, the pulmonary area lying in contact with Sibson's fascia at the root of the neck.

These three surfaces, so far as movements of the chest wall are concerned, are relatively stationary. The two surfaces of the lung which are directly expanded are the diaphragmatic and ventro-lateral or sterno-costal; these surfaces are the first to expand on inspiration, and it is only a residue of the expanding force which is left at the disposal of the more stationary surfaces. When one further considers that the lungs of young children are still lobulated and contain a considerable amount of connective tissue between the expanding areas, it will be seen, as I pointed out some years ago, that the expanding force of inspiration is spent to a considerable extent on tissue of little extensibility. There is thus in children an additional claim on the residual expanding force at the disposal of the stationary surfaces of the lungs after expansion of ventro-lateral and diaphragmatic surfaces.

If these are the conditions in normal respiration, how are they modified if the ribs are soft? It is a well recognized fact that the rickety deformity manifests itself most in those parts exposed to mechanical strain. The mechanical strain produces a deformity in the first place, and in the second place excites further rachitic softening by its irritation, thus producing for a time a vicious cycle of events. The thoracic distortion is characterized by an in-sinking of the chest wall in the upper part of the ventro-lateral region. Owing to the softening of the ribs the intrathoracic negative pressure has been able to prevent the expansion of the chest wall over the area of direct expansion. The consequence is that the only area of direct expansion is diaphragmatic, and clinical examination shows that this is really so. In cases of severe rickets the respiratory movements of the upper part of the thorax are scarcely visible, whereas the diaphragmatic contractions are relatively increased, with the result that the abdominal contents are depressed further than in the normal subject.

It must also be obvious that with the depression of the chest wall and the narrowing of the thoracic cavity, the surfaces of indirect expansion become atelectatic. In such cases one finds that the anterior borders of the lungs, as well as the posterior parts, lying in the hollow between the vertebral column and the ribs, are collapsed; the centers of the diaphragmatic surfaces of the lower lobes are usually emphysematous, only the narrow margin embedded between the diaphragm and the chest wall being airless.

Thus the pathological variation produced by softening of the ribs bears out Keith's contention as to the mechanism of normal respiration. But in what way does this variation affect the vascular system? The contractions of the diaphragm, which are increased in power and rhythm, exercise such pressure on the abdominal contents as to secure the flow of blood from the venous cistern to the heart. The pressure of collapse of the lung will mean that the negative force, which would otherwise be spent in dilating the infundibuli and alveoli, will be exerted on the vessels, so that the blood can reach the lungs with comparative ease, and it is in the lungs that the serious obstacle presents itself. The pulmonary circulation is secured by three great forces:

1. The driving power of the right ventricle.
2. The suction action of the left auricle.
3. The pumping action of the expanding and collapsing healthy lung.

In the rickety condition under consideration the latter two forces are thrown out of action, so that the whole work of propulsion falls on the right side of the heart.

The problem, however, which these cases present is not speculation as to the nature of complicated processes; it is rather to formulate what may be termed a "correlation of end results," and to answer the question, "Does the circulation suffer from diseased lungs or deficient thoracic movement?" Mackenzie emphasizes the importance of examining thoroughly the posterior aspects of the lungs as a guide to prognosis in cardiac disease. Extremely suggestive in this connection is his statement (under Onset of Heart Failure with Patients in Bed in chapter on Chronic Diseases of the Heart, Vol. II, Chap. XIII) that, "when the right ventricle is enfeebled, the assistance of the respiratory movements becomes necessary. When the patient lies in bed on one side, the pressure of the mattress on the ribs restrains their movement, so that the flow of blood through this part of the lung is retarded, and edema results. This can be shown in the early stages, for, when the patient breathes deeply, the whole of the crepitations may soon disappear." A correlation of the evidence in these four cases, which have just been described, leads definitely to the conclusion that the hypertrophied heart, with its broad, squat and globular shape, is the manifestation of an effort to compensate for the loss of accessory forces of circulation normally present in a healthy expanding lung and thoracic wall. Nor are these cases to be regarded as pathological curiosities. The variations present are only exaggerated examples of a condition, which is probably the determining factor in the issue of a large proportion of the fatal cases of so-called bronchopneumonia in underfed children, who are brought up in the overcrowded districts of industrial centers. In any case the observation of over 1,000 cases of measles, whooping cough and diphtheria has led me to the conclusion that, where an intercurrent bronchopneumonia extends over a period of a fortnight, the progress of the case has, as a rule, been complicated by the occurrence of collapse; in the case of non-recovery the patient has succumbed not to the toxic products of the infecting organism, nor to the noxious products of inflammatory decomposition, but to the severe mechanical strain which has been put on the heart. This strain is due to failure of the accessory pumping assistance of normally expanding lungs, and the almost constant occurrence of varying degrees of cardiac hypertrophy in such cases is very strong evidence in support of that contention. Similarly in acute rickets and in subsequent chest deformity there is great liability to collapse of lung tissue, more especially in the event of the occurrence of an intercurrent bronchitis. Such collapse enhances the disability to which the respiratory mechanism is exposed by the presence of soft rachitic ribs or a restorted and narrow thoracic cavity; the double embargo thus placed on the heart leads to an hypertrophy which can maintain compensation only over a limited period except under the most favorable conditions. The period of childhood and even of adolescence in cases of chest deformity may be occasionally survived without any considerable degree of inconvenience, and the result of excessive cardiac strain may manifest itself first in adult life.

However, it is not only in the bronchopneumonia and in the atelectasis of children that these mechanical considerations exercise a determining influence on the circulation. One not infrequently meets with cases of deformity of the chest, due to spinal caries or to collapse of the lung from old pleurisy, in which death has occurred with the signs and symptoms of cardiac failure. In these cases the heart is hypertrophied and exhibits the broad, quadrilateral shape described above. The embargo which has been thrown on the heart through the deprivation of the mechanical assistance of respiratory movements has led to a premature exhaustion of the circulatory system.

Rheumatism in Relation to the Circulation

It is comparatively easy to form a clear conception of the biological course of diphtheria or of typhoid fever or of syphilis. Every new experience of these diseases renders the conception clearer and more precise. With rheumatism the difficulty lies, not in the lack of material or experience, but, partly at least, in the loose and inaccurate way in which the term is applied to a variety of conditions which have no recognizable biological relationship to each other.

The terms "rheumatism" and "neuritis" are applied indiscriminately to a variety of complaints, whose only common feature is the feeling of pain. When and how this morass of confused thought and nomenclature is to be cleared up is not a subject for consideration here. But it is a remarkable reflection on the state of medicine that a series of complaints, so prevalent and fraught with so much discomfort and danger, should have so long escaped the concentrated attention, not only of research workers as a whole, but of general practitioners, who are, after all, in a much better position to recognize and valuate the symptoms of the protean manifestations of the disease. For, notwithstanding the abuse of the term and the insistent manner in which it is blamed for pains with which it has nothing to do, rheumatism is a disease whose histological basis, in many cases, can be easily identified, and whose manifestations in the form of articular, fibro-muscular and cardiac disease, present a fairly constant and typical clinical picture. One can but regret that Garrod's classical work, published now many years ago, should have failed to bear the fruit it promised, but it was in accord with the spirit of the times that the solution of the problem be relegated to the laboratory. It is not to detract from the real services of bacteriology to suggest that, in some respects, it has had a paralyzing influence on this particular branch of research. Inquisitive minds are set at rest by the publication of a discovery of the organism of rheumatism. It is alleged that the organism answers to Koch's postulates, and that its inoculation in animals is followed by arthritis, endocarditis and chorea. But arthritis and endocarditis occur in the human subject as a result of infection by streptococci, pneumococci, gonococci or meningococci; as for chorea, its etiology is obscure, and though present in some rheumatic subjects, it is associated with a variety of conditions with which rheumatism has no connection; the idea of experimental chorea in an animal is too ludicrous for discussion.

In the absence of a clear conception as to what rheumatism really is, and in the absence of an accurate and reliable method of determining which of the so-called "rheumatic" manifestations belong to that entity which is characterized by the distinctive histological reaction described in the case of rheumatic myocarditis and fibrositis, it is impossible to arrive at a satisfactory understanding of the relationship between rheumatism and heart disease. One not infrequently meets with cases of mitral stenosis in which there is no history or evidence of the associated phenomena of rheumatism. There is no evidence of arthritis, rheumatic nodules, chorea, or such other complaints as are generally accepted, with or without good reason, as an expression of a rheumatic diathesis. Blindly, and perhaps quite correctly, such cases are believed to be rheumatic in origin. There is, so far, no evidence to show that mitral stenosis may originate from any other common infections, such as pneumonia, diphtheria, enteric fever, gonorrhea or influenza. In 400 cases of scarlet fever, not a single instance was observed in which a valvular disease, comparable with that of rheumatism, arose during the period of infection, although there were in the series 4 cases of streptococcal endocarditis. There were two cases with heart disease on admission to the hospital, where the scarlet fever was followed by arthritis which appeared to be rheumatic rather than a result of the scarlet fever. In these cases an aggravation of the heart disease occurred.

The complexity of the problem cannot be illustrated better than in a brief reference to the association between rheumatism, chorea and endocarditis. In the course of an inquiry into the associated phenomena in chorea it transpired that, while chorea showed some relationship to rheumatism, it was much more frequently a motor disorder, related in some way to other diseases of the nervous system. It was found apart from rheumatism or apart from the history of any condition accepted as belonging to the group of rheumatic phenomena. It was found with pregnancy, organic brain disease, epilepsy, general paralysis, infantile paralysis, congenital mental deficiency, and with ailments of that ill-defined group which is said to exhibit the manifestations of neuropathic proclivity. It was also found unassociated with any other discoverable disturbance, functional or organic.

The Relation of Rheumatism and Chorea

The part played by rheumatism in the symptomatology of the cases under review was a very insignificant one, if the term "rheumatism" be restricted to the condition of acute febrile arthritis. Only in 3 cases out of 64 did the chorea develop in immediate association with acute articular rheumatism. In one case the chorea developed a few weeks after the rheumatic fever, and in the other two cases the two conditions were present simultaneously. In 18 cases out of the 64 there was a history of "rheumatism", but it is difficult to estimate the value which should be put on such a history. At any rate, so far as these cases are concerned, the part played by acute articular rheumatism was not a prominent one. It is possible, however, to miss the correct conclusion on this aspect of the subject by taking too restricted a view of the nature of rheumatism itself, for there are, no doubt, cases of chorea in which rheumatism is present in the form of cardiac disease or rheumatic nodules, and in which the articular form of rheumatism has never been present. At any rate, those cases of cardiac diseases which develop in childhood and in adolescence, and progress to a stenosis of the valvular orifices, sometimes show no sign of articular disease, and yet show other evidence of rheumatism in the form of nodules; and there is every reason to believe that when a case of chorea is complicated by cardiac disease, that disease is also rheumatic in origin. One must, however, avoid the error of assuming that rheumatic fever is a disease which is comparable with the ordinary acute infections, such as pneumonia and enteric fever. This is not the place in which to enter into a discussion on the merits of the respective theories which have been advanced to explain the origin and protean manifestations of rheumatism. It is sufficient to say that no conclusive evidence has so far been adduced in support of the microbic theory. I have examined ten cases of acute rheumatism bacteriologically, examining both the blood and the serous exudates, and I have not succeeded in isolating an organism. In two cases of recurrent rheumatism with advanced heart disease I have isolated a diplo-streptococcus, which produced arthritis and endocarditis in rabbits, but both cases were low forms of malignant endocarditis, superimposed on rheumatic endocarditis, and in each case the diagnosis was confirmed by post-mortem examination. If rheumatism is due to an organism, then that organism differs from the other organisms which produce acute febrile diseases, in that the subject of infection does not suffer from a disease which runs a definite course, and whose prognosis and complications can be explained in relation to the original infection. For example, in enteric fever the disease runs a definite febrile course, subject, naturally, to great variations, both in the character of the fever chart and in its duration, but the disease is almost always associated with a bowel lesion, and is almost always associated with some form of alimentary symptoms. The complications which occur, such as hemorrhage, peritonitis and bronchitis, can be brought into relationship with a perfectly clear conception of the pathological origin and course of the disease. With rheumatism, on the other hand, there is in the conception of its pathology no recognized starting point. It is certainly not primarily a joint disease, and many of its manifestations occur without fever. Some of its most definite signs, such as the erythemata, leave no recognizable anatomical lesion of a specific character.

Another point of contrast between the ordinary bacterial infection and acute rheumatism is that the latter in its several manifestations is amenable in so many instances to treatment with an ordinary drug like salicylate of soda. There is no instance of an infection outside of the protozoal group yielding to a drug of this kind. If chorea is to be regarded as bearing any relation to rheumatism, then that relationship is not a causal one. It is highly probable that the rheumatic state is capable of manifesting itself, whatever its cause may be, in a great variety of ways. In this respect it resembles more the character of a syphilitic or tuberculous infection. Its manifestations may run concurrently in some cases, and in others they may be mutually exclusive. The problem of the relationship of rheumatism to chorea does not resolve itself into a question as to whether any such relationship exists, but rather as to what the relationship actually is. In the cases which we have reviewed a direct relationship of a causal nature between the articular form of rheumatism and chorea certainly did not appear to exist.

The Relation of Cardiac Disease to Chorea

Cardiac disease was not a prominent feature in these cases. In 8 cases out of the 64 there was definite evidence of valvular disease in an advanced stage. In 10 other cases there was a mitral systolic murmur which might have indicated the presence of valvular disease, although it is quite possible, and indeed probable, that in some of these the murmur was functional in origin. In 4 cases a mitral systolic murmur was present during the attacks, but was absent when the patients were examined subsequently. In 3 cases the patients, during their first residence in hospital, showed no evidence of cardiac disease, but on admission for a second time there was evidence of cardiac disease. The irregularity of the pulse which occurs in some cases does not appear to have any relation to organic disease of the heart. In some cases it may be nervous in origin, and in others it is related to the respiratory irregularity incident to choreic involvement of the thoracic muscles. The peculiarly complex nature of the relationship which exists between chorea and cardiac disease is evidenced in the following case:

M. M., aged 62 years, was admitted to the hospital suffering from severe chorea, involving the arms, legs, face and trunk. The condition had lasted for a fortnight, and was associated with an acute inflammatory condition of the mouth.

Previous Health.—She was always of a nervous and excitable disposition subject to fits of temper and easily irritated. A year previously she had suffered from an acute inflammatory condition of the mouth, similar to that which is now present. It was supposed to be due to decayed teeth. Several teeth were removed, and a fortnight after their removal chorea supervened. For this she was treated in a hospital, and after three months' residence she was dismissed comparatively well. The choreic movements subsided, but in the intervening period between the disappearance of the movements of that attack and the onset of the present attack she had suffered from recurrent attacks of loss of consciousness, which, according to the story, present all the features of "petit mal". These attacks latterly came on every alternate day. Since the onset of her chorea on the present occasion the attacks of "petit mal" have ceased. She has never had rheumatism.

Family History.—Of three daughters, two have had chorea, one of them on two occasions, and the other on three occasions. This latter is also the subject of a mitral stenosis, although neither she nor any other member of the family has had articular rheumatism.

Condition on Admission.—The choreic movements were very exaggerated, but slow and of an athetoid type. The grimacing constituted, probably, the most marked feature in the whole picture. She was emotional and it was difficult to concentrate her attention. The tendon reflexes were exaggerated. There was no anesthesia of the skin. The mucous membrane of the tongue, cheeks and gums was swollen, and in places edematous. There were small ulcers on the gums. The mouth was evidently in a very painful condition. Her heart was normal. There was no other evidence of disease.

Condition during Residence.—The treatment during the first week of residence consisted in the administration of chloral and paraldehyde, and although sleep was induced, especially by the paraldehyde, the movements during the waking periods were not much diminished. In the second week of residence these sedatives were discontinued, and she was given 10 grains (0.65 gm.) of aspirin four-hourly, and from the time when the aspirin was commenced her condition began to improve, till now, at the end of six weeks' residence, she is almost well. In the disappearance of the symptoms the grimacing has remained in a more pronounced fashion than any of the other choreic movements. The mouth condition has from the beginning been treated with chlorate of potash and tincture of myrrh. The attacks of "petit mal" which were present during the interval between her previous attacks of chorea have completely disappeared since the beginning of the present choreic attack.

This woman, who was 62 years of age, developed a typical attack of chorea. She had never had rheumatism, and her heart was normal. Two of her daughters had had chorea in adolescence, but had never had rheumatism, either in the articular or in any other form, as far as could be made out; but one of them was the subject of a well-marked mitral stenosis, such as in the light of our present knowledge of cardiac disease would be naturally attributed to rheumatism. There is here not only the evidence of a deep-seated relationship between cardiac disease and chorea, but also the indication that it is the hereditary element, or neuropathic diathesis, which is the most general characteristic of chorea, indicating, as it does, the constitutional proclivity of the tissues of certain families to present the evidence of a certain group of lesions, some elements of the group appearing in some members of the family and some in others, and even in the case of a single individual different elements appearing at different ages. Garrod, in his well-known monograph on rheumatism, refers to the occurrence of chorea as a rheumatic manifestation in the following terms:

"Among the remaining manifestations for rheumatism which are specially common in children chorea holds a prominent place, and is often associated with endocarditis in cases in which the joints escape entirely. Without entering here upon the difficult question of the relation of chorea to rheumatism, the discussion of which is reserved for a later chapter, I may express my belief that the endocarditis, which in so many instances attends chorea affords evidence that in such cases the nervous symptoms are of rheumatic origin. I have more than once witnessed the development of subcutaneous nodules in association with chorea and endocarditis in cases in which there was no evidence of past or present articular troubles, and I believe that such cases afford very valuable evidence of the correctness of the above view.

"Chorea, like endocarditis, may be the earliest manifestation of the rheumatic state, but more commonly it appears as a later event in the series, either in direct association with, or as an immediate sequel of, more definite rheumatic attacks, or in patients who have suffered from articular rheumatism at some earlier period. Many rheumatic children exhibit a slight incoordination of movement, evidenced by twitching of the facial muscles or by some awkwardness of the hands and arms, which is hardly worthy of the name of chorea, and which may escape notice unless carefully looked for; and between such trifling symptoms and the most pronounced form of St. Vitus' dance every grade is met with."

The Relation of Rheumatism to Arthritis

There is no form of joint disease which by itself is clinically characteristic of acute rheumatism. Acute gonorrheal synovitis of the knee-joint may exhibit the same extensive appearances as acute rheumatic arthritis; the cytological examination of the exudate reveals no difference, although the gonococcus is easily cultivated from the former while the latter is sterile so far as present methods can show. Yet there is something in the appearance of the patient, in the odor of the exhalation from the skin and in the manner in which the inflammation moves from joint to joint, which constitutes a special feature of rheumatic disease; the response to salicylate of soda is, moreover, a test of some differential importance. There is, however, a form of arthritis associated with organic heart disease, in which the salicylates produce little or no effect either on the joints or on the temperature. These are cases in which the smaller joints, especially those of the hands, are involved. There is considerable pain, tenderness and interference with free movement, and the fever is irregular and seldom high. The condition may last for months and is most refractory to treatment; and in view of this, and of the other distinguishing features referred to, the question may quite legitimately be raised whether, in such cases one is dealing with a disease quite distinct in its etiology from that of which the ordinary acute articular synovitis is the outstanding expression. The presence of heart disease in both cases is not of itself conclusive proof of a common etiological basis. Information should be obtained to see whether on the whole the more indolent and refractory type is not more common in patients of a greater age. The presence of associated phenomena, common to the two types, such as rheumatic nodules should be looked for. One should not be content with the presence of tender spots which suggest nodules, but the nodules should be excised, a very simple procedure under a local anesthetic, and the histological character determined, before accepting evidence of their presence. The therapeutic reaction of salicylates is not of much value. The variability of syphilis in its reaction to mercury, and the contrast between syphilitic meningitis and general paralysis in their response to salvarsan prove how misleading the therapeutic test may be. It has not been our intention to attempt to give a systematic review of the manifestations of rheumatism, although this would be the natural and necessary introduction to a study of rheumatism of the heart. Rather have we found such a review in the present state of knowledge to be impossible. The fragmentary and patchy character of our observations constitutes a reflection of the unsatisfactory position in which the whole subject of rheumatism stands, and of the clamant need for a simple, systematic and thorough investigation. This must be carried out on lines which may determine the exact province within which a single causal agency may be operative as an etiological factor. Only in this way will it be possible to include or exclude those extraneous complaints which by use and wont and by abuse of nomenclature have found their way into the category of rheumatism. This is eminently a field for research on the lines and principles prescribed by Sir James Mackenzie in his recent publication. It is essentially the business, as it is the exclusive opportunity of the general practitioner, to observe the earliest subjective and objective manifestation; to watch its progress and varied expressions over years; to appreciate the importance or lack of importance of the factors of heredity and consanguinity; and to assess at its proper value the significance of the evidence of intermittent, predisposing or mutually exclusive ailments.

As a necessary adjunct and indispensable corrective to clinical observation and interpretation, the cooperation of the pathologist must be enlisted. The typical histological reaction in the rheumatic heart and in fibromyositis has been referred to already. In chronic cases it may be, and often is, equivocal, but in recent cases it is as distinctive and as characteristic as are the lesions of tuberculosis and syphilis for their respective infections. Much may be expected from the contributions of bacteriology and pathological chemistry. If an organism be the causal agent, then the histological basis suggests a microbe of a higher order than the bacteria and related to the tuberculosis or syphilis or malaria group and this suggestion appears more feasible in view of the frequent response to salicylates. Many of the phenomena suggest the presence of toxic agencies without the immediate presence of microbes; this applies more particularly to endocarditis, and the situation and character of the muscular and fibro-muscular lesions are not incompatible with a process of perverted metabolism of the muscle substance.

Whether the heart is affected by a poison produced by an organism localized in the region of the lesion as in syphilis, or whether it is affected by the toxins of an organism localized elsewhere as in diphtheria, or whether the inflammation occurs from a poison elaborated by metabolic perversion in the muscle as shown here and independent of microbic influence; these are questions for whose answer we look to the chemist and bacteriologist who work in intelligent cooperation with the clinician.

The Relation of Rheumatism to Heart Disease

Despite the somewhat nebulous notions which surround the problem of rheumatism, one is justified in the present state of knowledge in assuming that such valvular lesions as are not of syphilitic or pyogenic origin may be attributed to that process or disturbance which lies at the root of these allied conditions which are accepted as rheumatic. But it has been emphasized that the heart wall is also affected in the rheumatic states and to a degree or in a manner which initially, at least, is more serious than early involvement of the endothelium. Death may occur early in the course of acute rheumatism where there is evidence of circulatory failure which cannot be explained by valvular defect, but where the interstitial and subendothelial layers of the heart constitute the main seat of reaction, and where the fatal issue may be attributed to an involvement of the cardio-regulatory or vasomotor system. As a matter of fact the great majority of cases of rheumatic myocarditis run a prolonged course. Myocarditis, endocarditis and pericarditis may occur and recur over a period of years until the signs and symptoms of chronic heart disease have become established. The nature and solution of the problems which arise at this late stage are dealt with elsewhere.

It is estimated that the heart is affected in 20 to 30 per cent. of all cases of rheumatic arthritis. It is impossible to determine accurately in what proportion and what relative degree the pericardium, endocardium or muscle is involved. Generally speaking, the cardiac complications are more frequent and more severe in childhood and adolescence than in the later years of life. It is more than probable that the myocardium is involved in every case, and it is certain that the pericardium is much less frequently affected than the endocardium. The first evidence of cardiac involvement may appear in the second week of the disease, although as a rule the first symptoms appear at a later date, and may even exhibit themselves in the post-febrile stage and after the patient has been allowed out of bed. The first symptom is usually palpitation and a stabbing pain over the heart, or a feeling of tightness or oppression in the left breast. Sometimes the symptoms remind one of angina pectoris. On the other hand, the complaint may arise after walking or slight exertion and it may take the form of feelings of giddiness and pallor. In other cases, subjective symptoms are absent and abnormality of the heart is first detected on physical examination. The pulse may be rapid and soft, and occasionally irregular. The heart may be dilated both to the right and to the left and a mitral murmur may be present. Sudden exertion may give rise to breathlessness and cyanosis. On the other hand there may be weakness, pallor, rapidity of the pulse, and the other signs and symptoms which one associates with the sudden onset of cardiac complications in diphtheria. These cases are very infrequent but very serious. The aortic valves may be involved. It is impossible to determine the extent to which the myocardium and mitral valves respectively are affected, but it may be taken for granted that where dilatation is present the heart muscle itself is involved in the rheumatic process. While it is characteristic of diphtheritic myocarditis to proceed within a limited period to an issue one way or another, it is equally characteristic of rheumatic myocarditis to come to a temporary standstill but to be subject to recurrences at longer or shorter intervals. The acute stage may be complicated by acute dilatation due to exertion; by the freeing of excretions from the valves and the occurrence of embolic infarction; by the onset of pericarditis with effusion and the hampering of the cardiac function; or by vasomotor reflexes exercising a prejudicial influence on the peripheral circulation. Occasionally it is found that the regulatory apparatus in the heart itself is involved in the infiltration process and all stages of dissociated rhythm, from missed beats to heart block, may be met with. The tendency, however, in the great majority of cases is to an abatement of the acute process leaving the heart in a damaged condition which varies from a slight impairment giving rise to little disability on the one hand, to an impairment which may be so great as to lead to a permanent inability to respond to the more strenuous demands of life.

Treatment of the Circulatory Disturbances of Rheumatism

The treatment of the cardiac complications of rheumatism consists in the first place in the treatment of the rheumatic state. Salicylates and aspirin must be employed in the febrile stage, although the administration of those drugs does not necessarily prevent the later appearance of cardiac complications. It may be, however, that, if these drugs were employed to advantage for a sufficiently long period during and after the febrile stage, the possibility of cardiac complication might be diminished. It is advisable to employ diuretics in addition to antipyretics. Care should be taken in the regulation of diet and of alimentary excretion.

Most important of all is strict injunction regarding complete rest. The patient should on no account be allowed to leave bed. Emotional excitement of every kind should be avoided, not only during the progressive stage of the disease, but for months after the process has ceased. Where subjective symptoms are a feature of the complication counter-irritation should be applied over the cardiac region, and this may take the form of a blister which should be kept open for a week at least with stavesacre ointment (Unguentum staphisagriae of the British pharmacopoea). Instead of a blister an ice-bag may be employed, or alternative applications of heat and cold are frequently found to give relief.

In the period of convalescence the progress from the horizontal posture should be gradual. The patient should be allowed to sit up and the effect of the change of posture noted. Where the pulse is still rapid and small the change in posture should be made with great care. In getting out of bed and in walking the reaction of the circulation to increasing exertion should be carefully observed. Only after some time should walking on an incline be undertaken. When the period of convalescence and exercise in the open air is reached, altitudes over 1,000 feet should be avoided. Not infrequently one finds it necessary to treat a condition of anemia following the complication and this is best done with arsenic and iron. Where nervousness is a feature of the early or late stages of the complication the most useful sedatives are the bromide of ammonium and liquid extract of ergot. Digitalis and strophanthus, and the nitrites and similar drugs, employed in the more chronic forms of heart disease, are probably harmful in the acute phase of rheumatic carditis. Prophylactic measures may be taken in two directions. In the first place the patient should be warned to avoid conditions which are supposed to predispose to a recurrence of rheumatism. In the second place advice should be given in regard to the disability which has already been incurred. The extent to which physical and mental exertion should be incurred or avoided should be carefully prescribed, and this should be done in such a manner as not to prejudice the confidence and outlook of the patient. Not the least serious disability in many cardiac cases of organic origin is the neurasthenic state which probably originates in the presentation of too doleful a view of the condition.

Diphtheria in Relation to the Circulation

There is no infection whose toxins exhibit a predilection for the cardiac muscle in the same degree as those of diphtheria. It is estimated that ten to twenty per cent. of all cases of diphtheria which come under medical care show signs and symptoms of this complication. So far as the period of incidence is concerned, it is most frequent in the second and third week, but it occurs occasionally in the first week, and perhaps least frequently, though not least seriously, during convalescence, and from four to eight weeks after the initial symptoms of infection.

The character and varieties of anatomical changes in the cardiac structure have already been dealt with. It is impossible to correlate the differences in anatomical degeneration with the variations in clinical phenomena. This, of course, is due to the fact that in conditions of cardiac weakness the circulatory apparatus reacts as a whole and different states and stages of degeneration may present the same type of clinical phenomena. Generally speaking, the complications which occur in the first week, are associated with parenchymatous degeneration of the muscle, while those of the second and third week are associated with changes of an interstitial character in addition to those which affect the muscle fiber. The complications of convalescence are usually associated with interstitial reaction. It should be borne in mind, however, that the clinical phenomena depend not only upon weakness of the cardiac muscle but also upon profound vasomotor disturbances, which may be interpreted either as the direct result of toxic influence on the vasomotor apparatus, or which may be looked upon, as has already been suggested, as reflex phenomena of the nature of shock.

Symptoms and Signs of Circulatory Disturbance in Diphtheria

These may be varied and in the initial stages may give no indication of the seriousness of the complication. On the subjective side there may be little or no evidence of disease. Feelings of tiredness and oppression over the heart may be the only complaint; occasionally there may be something approaching an anginal attack, and there may be complaint of pain in the region of the liver. Loss of appetite, apathy and listlessness may come on with suddenness and this may be associated with a sudden striking pallor. If, in addition to these signs and symptoms, there be a slight arrhythmia, or extrasystoles, or an increase in the rate of the pulse accompanied by lowering of the tension, there may be little doubt that the heart has become involved. If these phenomena be associated with vomiting, not only is the diagnosis assured but the outlook may be regarded as more or less serious. Not infrequently a palatal paralysis in the second or third week is followed by a state of apathy and listlessness on the one hand, or of restlessness and agitation on the other. The patient is pale and vomiting is persistent; the pulse is either very rapid and feeble or very slow; there is no cyanosis and no edema; the liver is enlarged and pain is felt in pressing over it; there may be a trace of albumin in the urine. This state is indicative of the most serious form of cardiac complication, and not infrequently the symptoms remain without abatement for a few days and end in death. Less frequently there are one or more intermissions with recurrences and it is only very occasionally that recovery takes place. Edema and cyanosis are extremely rare, and it is only in the event of an associated nephritis that there is much albumin in the urine. The liver, on the other hand, is almost always enlarged. The interference with cardiac rhythm has been the subject of investigation on the part of those who are particularly interested in the pathological changes in the cardiac muscle which induce the various forms of irregularity. In an acute degenerative process like diptheritic myocarditis it is impossible to establish a definite basis between alterations in structure and abnormalities in functional activity. Heart complications may be associated with extensive degeneration of the musculature where there is only comparatively slight involvement of the auriculo-ventricular muscle bundle. It is practically certain that there are no cases on record where the bundle is involved to the exclusion of the rest of the heart. The profound vasomotor disturbances which are almost invariably associated with diphtheritic myocarditis cannot be left out of account in the estimation of the factors which predispose to the various forms of cardiac irregularity. Nor can one leave out of account the extra-circulatory factors which may ultimately exercise a determining influence on the adaptability of the circulatory apparatus. Palatal paralysis interferes with deglutition, more especially when vomiting occurs. There may be paralysis of the diaphragm associated with bronchopneumonia and the influence of all these contingencies undoubtedly contributes to a fatal issue.

It is estimated that thirty per cent. of the cases of diphtheria with cardiac complications die. Death may ensue in various ways. In the first place, it may occur with no premonitory evidence of disability. The patient, who, up to the time of death, has appeared perfectly well, may collapse and die suddenly after slight exertion. Very accurate attention to the progress of the disease might, however, in such instances, lead to the detection of apparently insignificant signs, such as occasional irregularities, tenderness of reflex origin in some parts of the left thorax, or diminution of urine. In the second place, the onset of the illness may be gradual; the pulse may become smaller and more rapid, and may then become extremely slow. The patient may be apathetic or restless and agitated, and in a few days, or in a few weeks at the outside, death occurs. In the third place, there may be recurrent attacks of collapse with precordial anxiety, dilatation of the heart and liver swelling, and this may be followed by a remission during which time the patient is perfectly well for a few days. This again may be followed by one or two recurrences terminating in death.

In the cases which recover there is also considerable variation in the clinical picture. In the first place, there may be a complaint of slight weakness with no change in the pulse-rate or tension and there may be a slight mitral insufficiency which can be readily overlooked. In the second place, there may be continuous or increasing weakness lasting from four to eight weeks, followed by gradual recovery. In the third place, there may be some symptoms for two or three weeks and the patient may get out of bed, then gradually become worse, and, after a further period of rest, may recover. In the fourth place, more severe forms which usually indicate a fatal issue, may, with careful attention and rest, pass from a period of great disability with occasional vomiting, collapse and all the other features of serious complications, and may ultimately recover. As a rule the patients who recover make a good and lasting recovery. There is a small residue in which weakness, slight cardiac dilatation with mitral defect, and arrhythmia in the form of extra systoles, are present for months or years, and may, in fact, last a life-time. It should be noted, however, that diphtheria does not, as a rule, produce the chronic cardiac weakness which is so characteristic of rheumatic myocarditis, nor is it associated with an organic defect of the valvular apparatus. In a very few cases there is permanent destruction of the muscle fiber as a result of early parenchymatous change and these patients, of course, suffer through life from a muscular defect. But whereas in rheumatism chronic cardiac disability with endocarditis as the most frequent sequela is often found, in the case of diphtheria myocardial disability is the exception and endocarditis does not occur.

Basis of Clinical Manifestations of Circulatory Disturbance

It has already been emphasized that it is impossible to correlate the various clinical manifestations with the variety, character and degree of the structural alterations in the heart. It is important, however, to recognize that the clinical phenomena arise from two sources; in the first place, from the weakness of the heart itself, and in the second place, from the disturbances of the vasomotor apparatus.

The disturbances which are due to changes in the heart arise both from destruction of the contractile substance and probably also from the irritating influence of the inflammatory reaction on the intracardiac regulatory apparatus, both muscular and nervous. Dilatation and mitral incompetence may be due to degeneration of the muscle substance as well as to interference with muscular tonus. The pallor, apathy, frequent restlessness, and the enlargement of the liver are ascribed to vasomotor disorders associated with a disturbance of the normal distribution of the blood in the body. There is probably an anemia of the brain as well as an anemia of the skin determined by the abnormal flow of blood to the abdominal viscera. The possibility of this aspect of the complication being due to shock has already been referred to. Whether or not a vagal paralysis is a contributory factor has not been definitely ascertained in spite of the fact that anatomical descriptions have been published which would indicate the possibility of this being the case. Care must also be taken of the secondary complications incident to paralysis, bronchopneumonia, aspiration pneumonia and nephritis.

Treatment of Circulatory Disturbance in Diphtheria

It is an open question whether the serum treatment of diphtheria tends to eliminate the possibility of cardiac affection. The probability is that the early complications, at any rate, might be avoided by energetic treatment, and it is almost certain that the earlier the treatment is undertaken the less likely are these complications to ensue. There can be no doubt that the amount of serum indicated by experimental test is not large enough to combat the more serious form of infection; that is to say, the amount of serum sufficient to neutralize experimentally a lethal dose of diphtheria toxin is not sufficient to produce the therapeutic effect of much larger doses. More severe types of diphtheria ought to be treated with at least 20,000, 30,000 or 40,000 immunity units in two or three doses. It is an open question whether in the case of later cardiac complications the repetition of serum is beneficial. There is always the possibility in the case of such repetition that anaphylactic shock may occur and contribute an extra burden to the circulation sufficient to produce disastrous results. Experience has not shown that digitalis, strophanthus, camphor and other remedies used in cardiac troubles are of use. Adrenalin is sometimes advised, and here again the influence of adrenalin on the vasomotor system is in some cases so profound as to be attended with danger in patients in which that apparatus is affected. Complete rest of body and mind, together with careful dietetic and hygienic arrangements, comprise the most important aspects of the treatment of these cases. Cold applications over the heart often give immediate relief; these may be alternated with hot applications. Great care must be taken in the convalescent period to regulate the gradual strain which is put upon the circulatory apparatus as the patient returns to health. Sufficient emphasis needs to be laid upon the importance of watching every case from day to day for the slightest evidence of any clinical phenomena which may indicate the approach of cardiac involvement.

Syphilis in Relation to the Circulation

The dermatologist is always on the outlook for syphilis and the neurologist usually keeps it in view. For the dermatologist it presents itself in a form which, though varied and often equivocal, has been more or less defined by experience, and he sees it at a stage in its development when the history and evidence of original infection may render diagnosis comparatively easy. The neurologist recognizes it to be the most common cause of organic disease of the nervous system, at least in middle life, and although its manifestations may be, in many cases, indefinite or anomalous, an examination of the cerebro-spinal fluid provides the means whereby the diagnosis may, as a rule, be placed beyond all doubt. On the other hand, the symptoms and signs of circulatory syphilis are very infrequent in proportion to the anatomical incidence of the complication, and when present, rarely indicate the nature of the process. This form of the infection is insidious in its onset and progress and may be present for years without giving rise to complaint. With the exceptions of aortitis and aortic aneurysm, coronary stenosis or cerebral endarteritis, which is usually a mistaken diagnosis for meningitis, the specific character of syphilis of the circulatory system usually evades the recognition of the clinician, although, from the very nature of its pathological character and course, the infection is more intimately associated with the circulatory system than with any other system of the body. The primary lesion manifests itself in the reaction of perivascular tissue and the organisms spread from the source of infection in the perivascular lymphatics. In the chancre the lymphatics are dilated and contain round cells. The walls of the veins and arteries are infiltrated, and later on, the endothelium of the arteries proliferates with still later narrowing of their lumina. The perivascular lymphatics, which drain the ulcer to the nearest glands, become hard and cord-like, and the glands themselves take on the well-known indolent induration which, when mixed infection is present, may lead to softening. It is in the clear bloodless sero-lymph pressed from the indurated base of the chancre or from the base of the papular syphilide that the spirochaetes can be most readily demonstrated. They may also be demonstrated in the clear juice of the indurated glands which drain the site of infection. Of low virulence and confined to spaces in which movements of the lymph are slow the organism gradually reaches the thoracic duct through the iliac lymphatics. In the very early stages they may reach the blood stream, but they do not survive in sufficient numbers to provoke a general reaction. It is only when they gain access in large numbers through the thoracic duct to the venous circulation that their general distribution determines an embolic spread which manifests itself in cutaneous lesions. Even this eventuality may be delayed or suppressed by the anti-syphilitic action of the gaseous content of the lungs and pulmonary blood which is known to be inimical to the life of the spirochaete. Once settled in embolic form in peripheral sites in the papillary layer of the skin the development of reaction proceeds again in the perivascular lymph spaces as it did in the original chancre. Certain tissues of the body exhibit a predilection for the spirochaete, harboring it and allowing it to manifest its pathological characteristics. Chief among these is the epidermal tissue of the skin and mucous membrane of the mouth and throat; and second in pathological affinity comes the central nervous system, which is developmentally related to the skin. It is during this period of combat with the blood, the period between the development of the chancre and the appearance of the rash, that the prodromal symptoms of the secondary stage are present. Headache, malaise, generalized pains and occasional fever are the subjective expressions of the reactions which occur prior to the appearance of the sore throat and the exanthem. Whether these later symptoms appear and how they appear depend upon individual properties of the host, and possibly, in some degree, also on variations in the infective agent.

It is thus seen that in the early stages of the disease the circulatory system is not only the vehicle but the site of infective reaction. The lymphatic and hemic circulations are concerned in the process and it is in the lymphatic transformations that the most important diagnostic reactions are discernible. The swelling and induration of the subcutaneous lymphatic nodules constitute one of the most important signs of the presence and progress of the disease in the early stage. The glands in the groin, in the posterior occipital region and the posterior portion of the sterno-mastoid region, the submental glands, and the epitrochlears, are those whose enlargement is of most importance to the clinician. In a primary lesion of the hand the epithrochlear will be enlarged; in primary affection of the mouth the submental gland will be enlarged, and it might be advisable in the absence of other determining evidences, for example, the failure to find spirochaetes in the suspected lesion, to excise these glands for spirochaetal and histological examination. It should be noted that the occipital glands may be enlarged from any irritation of the scalp and that primary infection of the cervix uteri is drained directly into the pelvis and not into the groin.

This conception of the secondary embolic spread of the infective agent may account for some of the visceral disturbances which occur in the secondary stage. The occasional incidence of acute nephritis, and of encephalitis, following both mercurial and salvarsan treatment, may be explained on the assumption that in these cases there has been an unusually extensive distribution of organisms by the blood stream, and that, whereas other viscera have resisted the settlement of infective colonies of spirochaetes, these organs have been unable to do so.

When, as a result of treatment, or less frequently as a result of natural resolution, the primary and secondary phenomena have disappeared there is no justification for believing that the disease has spent itself. In the absence of intensive treatment the virus remains in the lymph spaces and perivascular lymphatics and so far from lying dormant will tend to spread in a clinically latent form. This tendency will be proportionate to the absence or inefficiency of treatment. A year or even several years after the healing of the initial sore microscopic perivascular nodules may be detected in the site of the chancre. Similarly each papule of the papular syphilide is a diminutive chancre with an indurated base, distended lymphatics, perivascular infiltration, and proliferated connective tissue. In spite of intensive treatment it disappears slowly and its superficial disappearance may be deceptive. Months after such a rash has disappeared from sight it may be recognized by palpation, and even after it is no longer perceptible the presence of the lesion may be determined by histological examination. When the rash itself has disappeared its site retains in many instances the residual possibilities of further mischief.

The rupial and gummatous infiltrations of the skin which appear in the later stages are no doubt the reaction of dormant microbes whose activity has been only temporarily suspended. Apart from the latent nests in these sites the lymphatic spread may continue unnoticed in other channels. Without further skin or nervous manifestations the virus may spread slowly along the lymphatics and in later stages of the disease give rise to those aortic changes which are the prelude to aneurysm and syphilitic disease of the heart.

Coming to the actual diseases of the circulatory system whose origin is clinically attributed to syphilis, there is found that state of confusion which characterizes so many of the medical problems which are concerned with the relation of disordered structure to disordered function. Very extensive knowledge exists of the anatomical lesions of the heart and vessels due to syphilis, but the clinical conceptions of syphilis of the circulatory system are for the most part nebulous or inaccurate or both. While aortitis and aneurysm of the aorta are recognized as being due to this disease, myocardial involvement is regarded as a rarity. There is a very general disposition to attribute arterial disease, such as atheroma and arteriosclerosis with high blood pressure, to specific infection, although the most reliable anatomical investigations, for example those of Turnbull, definitely exclude the justification for such a view. On the other hand, early cerebral phenomena, such as hemiplegia due to meningitis, are attributed to endarteritis, whereas the arterial condition here is only the vascular accompaniment of the meningitis, and the disturbance is not due to lack of blood supply but to the irritation and pressure of exudation.

Relation of Syphilis to Arterial Disease

Turnbull's publication on arterial disease is but a short résumé of a very comprehensive and thorough study of the subject. It may safely be taken as a most reliable exposition on the problem, and its conclusions are confirmed by our own more fragmentary observations which have been carried out by clinical pathological comparisons. He divides arterial lesions into: (1) hypertrophies; (2) degenerations; (3) infiltrations; and (4) inflammations.

1. Dealing with hypertrophies he does not include under this designation the intimal or the adventitial hypertrophies, which are of inflammatory origin. He expressly confines himself to the well-known cardiovascular hypertrophies with high blood pressure, which involve both the heart and muscular arteries, frequently with incidental renal fibrosis. He states that an analysis of the cases does not afford evidence that the incidence of cardiovascular hypertrophy is greater in syphilis than in non-syphilitic cases.

2. In the degenerations he includes: (1) atheroma, which comprises all the varieties of primary intimal degeneration; and (2) the fatty, calcareous and fibrotic degenerations, which primarily and essentially involve the media. There is no evidence that syphilis is the cause of any one of those types of degeneration, and the medial fibrosis can be distinguished from chronic, syphilitic, medial fibrosis by the absence of inflammatory reaction

and by the absence of erosion of elastic tissue vessels and also by the absence of adventitial reaction.

3. Amyloid degeneration was present in 44 out of 7,924 consecutive necropsies, that is in 0.55 per cent. It was found in 5 out of 288 examinations in which lesions of acquired syphilis were present, that is, in 1.73 per cent. In 129 cases of chronic pulmonary phthisis in which intestinal tuberculosis was present it was found in 51; thus lardaceous infiltration of the vessels was found in 6.2 per cent. of cases of chronic phthisis of this type. In complicated and uncomplicated cases of tuberculous spine the percentage was 29.4, and in tuberculous conditions of other bones and joints the percentage was 16.6. It is thus quite clear that, although syphilis is a factor in the production of amyloid infiltration, its potency as such is not to be compared with that of osseous tuberculosis.

4. Blood vessels are not exempt from the infective reactions which involve other structures. These reactions may be due, on the one hand, to the organisms of suppuration such as streptococci or staphylococci or gonococci, in which cases the lesions do not present features characteristic of the infective agent; or, on the other hand, the lesions may be of a granulomatous character, and in such cases the reaction may be more or less characteristic of the microbe concerned. Thus syphilis, tuberculosis, leprosy, actinomycosis and rheumatism may give rise to arterial changes, which, though not always distinctive, are frequently indicative of the specific type of infection.

The spirochaete of syphilis is the most frequent and most important cause of inflammatory degeneration of the blood and lymph vessels. In early stages of the disease, as has already been pointed out, lymph vessels, veins and arteries constitute the chief sites of reaction. In the latter stages the aorta and the brain arteries are the seats of predilection for specific inflammatory degeneration. Vascular involvement in the early stage is part and parcel of the infection itself; it is indeed the local expression of the infection in the course of its development; but the diseases of the aorta and brain arteries in many cases constitute special degenerations attacking these special structures and comparable with gummatous degenerations of other organisms, such as bones, testicles or liver.

It is impossible within the scope of this review to enter into a consideration of the various inflammatory lesions of blood vessels. Suffice it to state that syphilis is the most important factor in inflammatory, vascular degeneration, and may occur: (1) as arteritis in the secondary stage in the brain, usually in association with meningitis; (2) as phlebitis or periphlebitis and venous thrombosis in the secondary stage; (3) as gummatous degeneration of large arteries, more particularly of the aorta, in the tertiary stage; (4) as gummatous phlebitis in the tertiary stage; and (5) as gummatous degeneration of the brain arteries in the tertiary stage.

Syphilitic Aortitis

From the point of view of the clinician the most important of these degenerations is syphilitic aortitis, which not infrequently involves the aortic valves and coronary arteries, and which is the most common cause of aortic aneurysm. There is considerable doubt as to the period intervening between infection and the commencement of aortitis. This is to be expected in a disease whose primary effects on the organism must be obscure. It is only when the aortitis has given rise to aortic incompetence or narrowing of the coronary arteries on the one hand, or to the pressure symptoms of aneurysm through weakening of the vessel walls on the other, that those processes which ultimately lead to symptoms really begin. These processes may themselves continue for a considerable period before symptoms make their appearance. Aortic incompetence may be made good by ventricular hypertrophy over years, more especially in those who pursue a sedentary occupation. Narrowing of the coronary arteries may also in such cases be present for long periods without giving rise to the distress which frequently accompanies this condition. Aneurysmal dilatation of the aorta may exist for years without giving rise to those special symptoms which are the usual source of its discovery. As a matter of fact, histological examination of the walls of a syphilitic aneurysm shows in the majority of cases that the infection has spent itself or is in a quiescent state. Turnbull was able to determine the length of interval between primary infection and death in 32 of his cases. The intervals were as follows: 7 years, 1 case; 8 years, 2 cases; 15 years, 2 cases; 17 years, 1 case; 20 years, 4 cases; 21 years, 3 cases; 22 years, 3 cases; 24 years, 2 cases; 25 years, 3 cases; 26 years, 3 cases; 28 years, 1 case; 30 years, 1 case; 38 years, 1 case; 39 years, 1 case; 40 years, 4 cases. There is, however, no indication of the interval which as a rule elapses between infection and the onset of the degenerative changes. This interval is presumably shorter than is generally supposed.

As to the syphilitic nature of the aortitis in question pathologists are generally agreed. Its predilection for the ascending part of the aorta, its relative infrequency in the abdominal aorta, the characteristic star-like cicatrization of the intimal surface, the thinning of the media through destruction of elastic tissue, and the adventitial infiltration with involvement of the vasa vasorum, are, as a whole, typical anatomical features of the disease. The frequent association with other anatomical evidences of syphilis is confirmatory of its nature. Not only is syphilitic aortitis the most common complication of the aorta, but it is the lesion of acquired syphilis most commonly found in the post-mortem room of the general hospital. In these cases the Wassermann reaction is positive as a rule.

The following is an analysis by Turnbull of his 288 necropsies in which the lesions of acquired syphilis were found. Turnbull's observations show the presence of syphilitic lesions of the body in 4 per cent. of his total cases. This, of course, is a smaller proportion than the general incidence of syphilis in the hospital population would indicate. It may be assumed from clinical experience that 10 per cent. to 15 per cent. of these patients suffer or have suffered from syphilis. But from the chronic nature of the disease, and also taking into consideration that Turnbull's material includes few cases of nervous syphilis and no cases of congenital syphilis, his figures probably represent an incidence which is compatible with the estimate of an infection of 10 per cent. to 15 per cent. on the whole. Even if such a percentage of infection be present in hospital cases at one time or another, Turnbull's figures would show that 25 per cent. to 30 per cent. of these cases developed aortitis; and of these cases in which organic lesions were found in a post-mortem, 60 per cent. showed evidence of aortitis.

We are not here concerned with the factors which render the thoracic aorta more susceptible to syphilitic inflammatory degeneration than other arteries of the body. It is pointed out, however, in this connection that the aorta has to bear the greatest strain of the extra-cardiac circulation, and the nearer the heart the greater the strain. It should not be overlooked, however, that in many instances the disease stops abruptly at the diaphragm, an important fact in distinguishing syphilitic aortitis from atheroma. This sharp delimitation of the disease to the thoracic aorta would suggest that some part is played by the variations in intra-thoracic pressure. These, however, are points of speculative interest only and our concern is more with the clinical results of aortic disease. It carries in its train, or is associated in its development with (1) aneurysm, (2) endocarditis, (3) narrowing of the coronary arteries, and (4) myocarditis.

1. Aneurysm may, of course, arise from causes other than syphilis. Acute inflammatory endocarditis may spread to the aortic wall and cause a weakening which may give rise to an aneurysm. Congenital defect in the development of the aortic arch may occasionally give rise to aneurismal dilatation. Advanced atheroma is sometimes also a predisposing factor. Syphilis is, however, the commonest cause, and in all the 175 cases of syphilitic aortitis observed by Turnbull there were shallow sulci and pits or diffuse or saccular aneurysms, and in 54 of these cases, that is, in 30 per cent., there were aneurysms inducing clinical manifestations, including aneurysmal stretching of the commissure.

Syphilitic inflammation is the most common cause of aneurysms in other large elastic arteries. Such aneurysms arise as a rule in close proximity to the origin of the arteries from the aorta. They are rarer, however, than aortic aneurysms. Turnbull found aneurysmal pitting or pouching in all 43 cases of aneurysm of the large arteries which he observed, with the exception of a case of arteritis of the second branch of the pulmonary artery.

Aneurysms exhibiting clinical manifestations were present in 5 of these, that is, in 11.6 per cent. Their sites were, 3 in the innominate artery, 2 in the right common carotid, and 1 in the left subclavian.

2. Aortic endocarditis is a frequent sequel or accompaniment of syphilitic aortitis. Turnbull found this condition in 45 cases out of his 175, that is, in 15.6 per cent. Where the aorta is the seat of valvular incompetence in a patient whose cardiac disability commences in middle life, and in whose case there is no evidence of the expression of rheumatic diathesis and no history of organic disease of the mitral valve, the condition in the great majority of cases may be regarded as syphilitic.

3. Where endocarditis is present with aortitis there is not unusually a narrowing of the lumina of the coronary arteries. Such narrowing may be sometimes found at the aperture, or in the form of a constriction a short distance from the aperture. There may be even complete occlusion of one of the coronary arteries. This condition gives rise to a nutritional fibrosis of the cardiac muscle which is not so much a source of danger in itself as an indication of the impoverishment of the heart as a whole. It is one of the most common causes of sudden death from cardiac failure, the terminal phase being probably a state of ventricular fibrillation. Diminution in the caliber of the coronary arteries is also recognized as a cause of anginal attacks.

4. The cardiac muscle is the seat of syphilitic degeneration far more often than is commonly recognized. Large gummata occur seldom, but syphilitic inflammatory infiltration and fibrosis can be easily detected by microscopic examination in a large proportion of cases in which aortitis and endocarditis are present. Where the inflammatory reaction is recent spirochaetes can be detected; it is impossible, however, to assess the clinical importance of such myocardial changes. The histological evidence of the disability is usually found in the perivascular tissue and in the subendocardial connective tissue. The amount of muscular destruction cannot be said to be such as to give rise of itself to cardiac weakness or to compensatory hypertrophy as is generally supposed. As a matter of fact, if one excludes the acute myocarditis of diphtheria and less common myocarditis of enteric fever there are practically no conditions of myocardial degeneration which, of themselves, account for cardiac weakness. In syphilis of the myocardium the aortic valves and coronary arteries are usually involved, and it is to this rather than to destruction of muscle that the symptoms are to be attributed. In this respect syphilitic myocarditis does not differ essentially from other forms of degeneration of the ventricular myocardium.

Syphilis of Large Muscular Arteries

Syphilis of the large elastic branches of the aorta is much rarer than aortitis and is practically invariably associated with that condition. Syphilis of the large muscular arteries is rarer still, and in his series of 288 cases of syphilis, Turnbull observed it only five times. On each occasion aortitis was also present and it was found twice in the celiac arteries, once in the superior mesenteric, once in the celiac and superior mesenteric, and once in the splenic artery. The structural alterations corresponded with those observed in aortitis.

Syphilis of the Small Muscular and Elastic Arteries

The smaller arteries are involved in all the structural reactions of syphilis which are proliferative or gummatous in character. The arterioles and smaller arteries are usually affected in the neighborhood of gross syphilitic lesions. The basal arteries of the brain are, however, the vessels of moderate size which most frequently exhibit characteristic changes. Microscopically they are of a white, pearly appearance, round and cylindrical, and of a firm consistence and distinguishable from atheromatous vessels by the absence of calcification or caseation on their inner surfaces. Where caseation is present in these arteries it is on the outer surfaces and this may be determined by incision. It may also be remarked that in the case of syphilis, especially of recent date, the arachnoid is adherent. In recent cases microscopic examinations show the pathological process in the arteries to be confined to the adventitia where small masses of lymphocytes are spread in nodular form over the media. Occasionally neutrophilic leucocytes and microbic masses may also be observed. A few leucocytes may be scattered through the media. The intima is usually the seat of extensive proliferative changes. This intimal proliferation is usually distinguishable histologically from the intimal hypertrophy or diffused arteriosclerosis with medial hypertrophy and ultimate medial sclerosis accompanied by enlarged heart and high blood pressure. In this latter condition the muscular and elastic fibers have a regular arrangement, whereas in the granulomatous hypertrophy of the intima in syphilis, and in other granulomata, the connective tissue and elastic fibers are irregularly dispersed. Even where an elastic ring appears on the inner surface of the hypertrophied zone the appearance is quite different from an arteriosclerosis' hypertrophy. In the cerebral arteries of recent syphilitic infection spirochaetes have been demonstrated in the vessel walls. Cases occurring within six months of infection have been published. Benda had a case fifteen months after infection and Strassman has recorded a case of meningo-encephalo-myelitis in which numerous spirochaetes were found in the walls of vessels of both brain and cord; in this case the infection occurred a year and nine months before death.

Syphilis of Veins

Attention has already been drawn to the involvement of the venules in the site of primary infection and also of those which lie on the route of infection from its source. The venules are also affected in the cutaneous lesions, more especially in the papular syphilides and late secondary lesions of the ulcerative type. They are also involved in the vascular disturbances associated with recent brain syphilis. The pains of a "rheumatic" character, which affect more particularly the lower limbs in the secondary stages are probably in some cases due to phlebitis. Tender cord-like thickenings of smaller veins are not infrequently observed, and it is not impossible that the persistent tendency to thrombosis after injection of salvarsan in some cases may have its origin in this complication. We have observed cases in which such thrombosis occurred on two or three successive occasions and in which there was no question of faulty administration. In these cases the patients complained of dull pains in the limbs and of tenderness on pressure over soft parts. Phlebitis of the secondary stage is characterized anatomically by polymorphic infiltration of the adventitia and of the intima with occasional thrombosis. In many respects it is similar to the tertiary phlebitis, which, however, is frequently associated in addition with periphlebitis of a gummatous character showing a tendency to liquefaction. It is of great importance to note that not a few of the so-called varicose ulcers of the lower limb are syphilitic in origin and yield readily to antisyphilitic treatment when other measures have proved fruitless.

Clinical Manifestations of Syphilis of the Circulatory System

Early Symptoms.—Complaints which have reference to the heart are occasionally made by patients in the early and more acute phases of the infection. These complaints have not an organic basis exclusively confined to the heart or circulatory apparatus. They are indistinguishable from the corresponding phenomena incident to other infections and toxic processes which exercise a debilitating influence on the economy as a whole. There appear also in some subjects of syphilis, who are of a nervous or hypochondrical disposition, disturbances of sensation and disordered feelings which are, in the first instance, referable to the heart, but which are really the expression of emotional instability aggravated by fear of the infection and anxiety as to its consequences. These toxic and nervous disabilities tend to disappear with the success of the specific treatment, and by the assurance which is an indispensable adjunct to all successful therapy.

Phlebitis.—Early syphilitic phlebitis, which has just been referred to, is the involvement of the circulatory system which gives rise to symptoms based on definite anatomical lesions. The condition is comparatively infrequent and may be readily overlooked. The pains are generalized and are not acute; they are passed over as "neuritic" or "rheumatic", like so many other pains of unknown origin. They disappear with the subsidence of the acute secondary symptoms. Early phlebitis does not give rise to acute inflammatory changes or to liquefaction, and we have not observed thrombosis of larger veins in the early stages except as a result of the traumata of venepuncture after salvarsan administration. The relation of varicose ulcers to syphilis has already been referred to.

Arteritis.—Syphilitic arteritis occurs as a rule, if not exclusively, as part of a more general specific lesion. It may be present in practically every syphilitic reaction, in chancres, secondary nodular gummata and in meningitis. It reaches its greatest importance in an etiological sense in the cerebral arteries associated with meningeal changes. Here it may of itself exercise an independent influence when occlusion is extreme by interfering with nutrition. This is more especially the case when the smaller arteries of the basal nuclei are involved. These arteries do not display the free collateral arborization characteristic of the larger branches of the circle of Willis, and so obstruction to free flow of blood in them may lead to depression of activity if not to complete destruction of some vital center in the basal structures. When the clinical phenomena point to lesions of the cerebrum, especially in monoplegia and hemiplegia in the late secondary stage, the symptoms are probably due not to occlusion of arteries but to pressure of exudate, and in this case early treatment offers a better prospect than in those cases in which basal tissues are affected. Reference has already been made as to the variety of ways in which brain syphilis may supervene. In the majority of cases the lesions are probably mixed and in practically all the vessels participate. The clinician may be satisfied when once the specific character of the disease has been determined; to proceed to a more definite diagnosis on clinical data alone is to indulge in guess-work which, however, may be more or less intelligent according to experience.

Aortitis.—The frequency of syphilitic aoritis has been emphasized. It is recognized as of the greatest importance to the pathologist in the elucidation of the structural disintegration leading to death. Insidious in its onset, vague in its symptomatic expression, it develops as a rule in such a manner as to elude even the suspicion of the clinician until the circulatory apparatus has been involved in irreparable damage. It is far advanced on its course before it gives rise to aneurysm with its concomitant symptoms of pressure. It involves the coronary arteries and the aortic valves before the patient seeks advice and the myocardium degenerates from exhaustion or from failure of nutrition before successful therapy can be adopted. It is rarely recognized within the first ten years following infection and the majority, 17 out of 31, of Turnbull's cases came to post-mortem between twenty and twenty-six years after the primary symptoms.

Disease of the aorta may, of course, occur in parts at a distance from the heart and give rise to pressure symptoms of aneurysmal dilatation without directly involving the efficiency of the heart itself. When severe cardiac symptoms are present, disease of the heart and vessels cannot be distinguished, and the organism has already become involved in a complex in which biological adjustment has been strained to the breaking point before the patient seeks advice. Premonitory symptoms of a vague character may, in some cases herald the stage of irremediable disability. Feelings of discomfort and abnormal sensations in the heart region, occasional attacks of palpitation, indefinite pains and sensations of pressure in the breast with weakness and anxiety may occur in varying degrees of severity over considerable periods prior to the establishment of the well-defined symptoms of angina pectoris. Mild emotional depression and hypochondriasis may constitute the psychic coloring of the picture, although in the presence of such symptoms the possibility of early general paralysis should not be overlooked. Even in the absence of a history of syphilis, with the foregoing symptoms in a man of thirty to fifty years of age of anemic or cachectic complexion, the associated phenomenon of syphilis should be looked for. Aortic incompetence without organic complication and the absence of a history and the expression of a rheumatic diathesis are important considerations in a man of that age. The conditions of the pupils and deep reflexes should be ascertained and the presence or absence of scars on the throat or base of the tongue, or the presence of scars and healed ulcers on the lower extremities should be determined. A Wassermann test should be done and a radiological examination of the chest should be made.

Even after the syphilitic basis of a cardio-aortic complaint has been determined it is practically impossible for the clinician to interpret the precise nature of the anatomical lesion. This difficulty is due to the fact that the structural alterations involve as a rule more than one function of the parts affected; an aortitis with aneurysmal dilatation may embarrass breathing by pressure on a bronchus; the aortic valves may be incompetent and such incompetence may give rise to symptoms incident to that defect; the coronary arteries may be involved with consequent malnutrition of the heart and weakness of the muscle, followed by deficiency in the general circulation and anginal attacks due to coronary narrowing.

Syphilis of the Myocardium

Gross syphilitic lesions of the myocardium do not occur; that is to say, there are no diffuse syphilitic degenerations of the myocardium comparable with aortitis or with cerebral syphilis as seen in general paralysis. The nearest approach to such conditions is the diffuse interstitial fibrosis which is sometimes observed in congenital cases. In acquired syphilis isolated gummata have been described. These may give rise to no symptoms, while, on the other hand, sudden and unexpected death has been attributed to their presence. Diffuse granulous proliferation may occasionally be seen in perivascular areas and beneath the endocardium, and in these lesions spirochaetes have been demonstrated. In late cases this actively proliferating tissue has become fibrosed. The muscle fibers are not seriously involved in these perivascular and subendocardial changes.

The function of the myocardium is prejudiced to a far greater extent by narrowing of the coronary arteries in aortitis than by any form of direct syphilitic involvement of its structure. This is more especially the case where there is aortic incompetence with its concomitant low blood pressure during diastole. When the double defect of narrowed coronaries and low blood pressure is present, the part of the myocardium supplied by the terminal branches of the longest vessels becomes fibrosed from lack of nutrition and such fibrosis is not so much a source of weakness in itself as an evidence of general impoverishment of the whole organ. Syphilis of the heart then, when it occurs, gives rise to symptoms which are usually due to a complicated lesion or series of lesions which cannot be interpreted on clinical evidence alone, and which involve not only the myocardium but also the aorta and coronary arteries.

There is one condition, however, in which a localized lesion, generally syphilitic, gives rise to a definite clinical picture, and that is Stokes-Adams syndrome or heart block. Complete auriculo-ventricular dissociation may occur in diphtheria or more rarely, in rheumatic fever, or, perhaps more rarely still, in septic endocarditis or influenza. But in the absence of these acute infections, heart block in a person of advanced years is, as a rule, due to syphilis. The clinical phenomenon depends primarily upon destruction of the auriculo-ventricular bundle as it passes through the septum fibrosum before its division into the main right and left branches. The septum lies immediately beneath the aortic valves, and when syphilitic aortitis and endocarditis spreads onto the septum the bundle may become involved in the degenerative process. In some cases the main bundle itself may escape and either the right or left branch or both may be independently severed, after their separation from the main stem. The main clinical features of the condition need only be mentioned here; slow regular pulse 20 to 40 beats a minute as a rule, the auricles beating independently and more rapidly, or in some cases, fibrillating or fluttering, and with this slow ventricular rate the occurrence of epileptiform seizures. In some cases the block is probably incomplete at first, but at this stage it is not likely to come under the notice of the physician. It should be noted, however, that complete heart block may occur in advanced cases of atheroma of the aorta where the degenerative processes which show no trace of syphilis spread from the vessel walls to the bundle.

Treatment of Circulatory Disturbance of Syphilis

By early and thorough treatment of the infection when it is recognized in its initial stages, the occurrence of circulatory complications will usually be avoided. These complications may, however, occur in some cases in which the early phenomena have been ephemeral, or in other cases in which the disease has run a latent course. In any case, in the majority of those conditions, irreparable damage, involving impairment of function, will have resulted before a diagnosis can be made, or even before the physician is consulted. The therapeutic procedure will depend on the nature of the particular manifestation of syphilis which is presumed to be present.

1. Early lymphatic and perivascular infiltrations will disappear in the course of the primary treatment, which should include intensive administration of both salvarsan and mercury.

2. Cerebral arteritis (or meningitis) of the late secondary stage should be treated with doses of salvarsan, beginning with 0.1 gram and gradually increased to 0.4 gram until a total of 3 or 4 grams has been given. Mercury should also be given and the result controlled by examination of the blood and cerebrospinal fluid.

3. Late cerebral arteritis (chronic meningitis) should be treated by the initial administration of mercury and iodides for a fortnight, to be followed by gradually increasing doses of salvarsan, the mercury and iodides to be continued meanwhile and the results controlled by examination of the blood and cerebrospinal fluid.

4. The greatest precaution must be observed in the treatment of aortitis and its coronary and myocardial complications. Preliminary measures of a hygienic and dietetic character must be taken before recourse to the administration of salvarsan. The general condition of the patient must be such as to preclude the possibility of circulatory failure incidental to the vasomotor disturbances which occasionally follow salvarsan injection. The efficiency of the circulation must be restored to as great an extent as is compatible with the nature of the lesions. Iodides and mercury should be administered orally for a period of a fortnight, and, following this, an injection of 0.1 gram of salvarsan may be given. This should be repeated every three days for a fortnight, when the dose may be increased to 0.2 gram. In no case should more than 0.2 gram be given at a time. Careful observation should be made to note the possible advent of a vasomotor reaction during the injection. This is heralded by a change in the quality of the pulse, which takes on a bounding character

and increases in rapidity, and also by a flushing of the face. If any of these phenomena appear, injections should be stopped immediately. The accessory treatment employed in cardiac syphilis with coronary disease, aortic regurgitation, or angina should be continued.

(5) Varicose ulcers or chronic phlebitis of the latest stages should be treated with salvarsan and mercury in the ordinary way. In a case of chronic varicose ulcer, excellent results are obtained from the local application of gauze soaked in a 1 in 30 solution of alkalinized salvarsan. This may be alternated with the local application of fresh human serum applied in the same way.

Acute Infectious Endocarditis

Acute infectious disease of the heart occurs as a complication of generalized septic infection. The endocardium, and particularly the valvular endocardium, is almost exclusively the main seat of the reaction. Occasionally there is pericarditis; but, although there may be multiple septic emboli in the muscle, the lesions are not, as a rule, such as to produce obvious clinical disturbances, except in those cases in which there is an extensive spread from the valves to the adjacent myocardium.

On the whole, infective endocarditis is a particularly rare occurrence and it is perhaps most frequently seen as a complication of the septicemia incident to some cases of septic puerperal infection, where the vascular system is invaded by septic thrombi from the uterine veins. It may occur, also, as a sequela of croupous pneumonia and when this occurs the onset, as a rule, follows the crisis after an interval of two or three days. It may also occur as a complication of septicemia which has originated in a furuncle of the skin. It is a rare complication of gonorrhea and of epidemic meningitis.

The cardiac lesion varies, as a rule, with the character of the infecting organism. In pneumococcal endocarditis and in streptococcal endocarditis there is usually a shaggy, fibrinous deposit composed of large masses of fibrin, necrotic material and organisms on the valves. In the milder forms of infection the fibrin may be very small in amount and the lesion may be more of the character of a spreading ulcer. The aortic valves are more frequently involved than the mitral and the right side of the heart much less frequently involved than the left. The ulcerative process may spread into the adjacent portions of the heart rupturing the tendons of the valves, involving the bundle of His and extending into the wall of the aorta producing aneurysm, and even rupture. The opening of the coronary arteries may be involved by the spreading masses of fibrinous exudate. Incompetence of the valvular apparatus may occur as a result of rupture of the valves, although it has been noted that valvular incompetence is not so frequent clinically as one would otherwise expect. The infection may find a site on the base of an old endocarditis, where the vascularized tissue of the valves with the wide lymph spaces constitutes a favorable seat for infective reaction.

The origin of the disease is as a rule easily discovered. Puerperal fever, pneumonia, furuncle of the skin, mastoid disease and septic joints or septic bone lesions indicate the probable source of the series of phenomena in which septic endocarditis finds an expression. With regard to the organisms of infection it may be noted that streptococci are most frequently present, next in order of importance come pneumococci and gonococci. With regard to the streptococcal group, it has been noted that the variety composed of long thin chains is the most malignant, whereas the short chain variety, probably of bowel origin, is the least malignant, and it is important where the question of malignant endocarditis arises, to make a bacteriological examination of the blood.

Clinical Phenomena of Acute Infectious Endocarditis

The patients are as a rule healthy and in middle life. The initial symptoms frequently do not point to the heart. There may be complaint of pains in the joints, general weariness, difficulty in breathing and occasionally diarrhea. In the more chronic types recurrent fever of a doubtful origin, progressive anemia and albuminuria constitute the main objective symptoms.

In the beginning of the illness the fever may rise gradually and it may be irregular, and it is only in the later stages of the more acute types that it is characterized by recurrent rigors and sweatings which are probably an indication of generalized embolic infection. There is, of course, that type of septic endocarditis, which, in the temperature chart resembles malaria, but one should not be misled by the supposition that all, or the majority of cases of malignant endocarditis, have a temperature curve of that type. A period of a week with insignificant and irregular rise in temperature may be followed by recurrent rigors lasting for two or three days, and again the temperature may resume an irregular and equivocal character. The pulse in the majority of cases follows the temperature curve, although in some instances it may be correspondingly more rapid and in others relatively slower.

The spleen is usually enlarged and soft and only in long standing cases is it of that hard consistency which renders palpation easy. Occasionally the liver is swollen. The alimentary canal is sometimes the seat of embolic ulcers and associated with these one finds alimentary disturbances, loss of appetite and diarrhea of a dysenteric character.

Almost a constant feature of septic endocarditis is the occurrence of an associated nephritis, although this complication, as a rule, passes without producing the clinical phenomena one would expect. This is due to the fact that the nephritis is not of the ordinary type but is of the character of glomerular nephritis and only in exceptional cases so invades the mass of renal tissue and interferes with its function to such an extent as to interfere seriously with elimination. Edema and uremia are rare complications of septic endocarditis. Among the most important clinical phenomena are the erythemata or small hemorrhages which occur in the skin. These skin hemorrhages are of great diagnostic importance. They are more frequently found on the lower extremities than on the upper extremities, and are very seldom found on the face and neck. They vary in size from one-eighth to one-fourth inch in diameter. The center is distinguished from the circumference by a gray necrotic appearance and sometimes by a small abscess. Hemorrhages may also be found in the retina and these vary according to the size of the vessel involved.

The character of the blood is changed in a manner corresponding to the alterations observed in general septic states. Leucocytes are sometimes increased. The number and quality of the red blood corpuscles are altered and as the disease progresses anemia dominates the picture.

It has already been pointed out that the initial symptoms may begin in the joints. They become red and painful, and in some instances resemble the condition seen in an acute rheumatic arthritis. It is often extremely difficult to distinguish the one condition from the other. As a rule, however, the salicylates have an immediate effect on the rheumatic state, whereas they have practically no effect on the septic complication. Bacteriological examination is the most certain clue to differentiation. Only in rare instances do the joint complications develop to a purulent stage.

The mental state of the patient varies from a condition of mild excitement with a feeling of well-being to a condition of restlessness with delusions and even transient loss of consciousness. The characteristic feature of the advanced stage of the disease is that in which the patient, although looking very ill, admits to a feeling of well-being.

The foregoing description applies to a state of general septicemia quite apart from a cardiac complication. There may be even a very advanced state of valvular degeneration with only slight clinical evidence of cardiac disease. So much so is this the case that advanced cardiac complications may run to a fatal issue without producing signs or symptoms which would definitely relegate the lesion to the heart. All the associated phenomena in a case of this kind should be taken into consideration and carefully weighed. The previous history of the patient with regard to infection and the exclusion of other febrile infectious states, such as miliary tuberculosis and typhoid, which might present a similar clinical picture, must be considered. Bacteriological examination of the blood should be made and, if negative, should be repeated, for in the more indolent type of case several examinations may be made with negative results.

Embolism.—The occurrence of rigors is an indication of the detachment of parts of valvular excrescences and the spread of infection by embolism. Embolism is one of the most important indications, when it occurs, with septic endocarditis; it is not clinically, however, a constant complication. The petechial eruptions of the skin have already been referred to, as also retinal embolism which has been known to give rise to a purulent panophthalmia. Renal inflammation is probably the most frequent form of embolic spread and is associated with hematuria, and is to be regarded as a glomerular nephritis due to the embolic spread of bacteria which colonize in the renal glomeruli. Embolism of the alimentary tract gives rise to diarrhea, and splenic embolism to pain and friction in the splenic region and occasionally to septic peritonitis. Cerebral embolism may also occur giving rise to various localizing symptoms, hemiplegia, monoplegia and affections of vision and hearing. Very occasionally the large arteries of the extremities are the seat of embolism followed by purulent inflammation and gangrene.

Atypical Cases.—Reference has already been made to the difficulty in diagnosing the more indolent forms of septic endocarditis which may run its course for months, or even for a year or more. One case was observed in which pneumococcal endocarditis following pneumonia passed into a state of abeyance with complete absence of symptoms for six months, and this was followed by a recurrence which was fatal. Not infrequently one meets with obscure cases of nephritis associated with intermittent temperature and anemia, and these, after running a course of months, are recognized, perhaps for the first time on the post-mortem table, as cases of endocarditis. The infecting organism in such cases is usually a short diplococcus or diplostreptococcus of low malignancy and corresponding in its bacteriological features to a form of bowel streptococcus. In other cases the main clinical manifestation of obscure septic endocarditis is to be found in an intractable and varying arthritis. In these cases bacteriological examination of the joints may give a clue to the nature of the infection, and yet the cardiac symptoms may be so equivocal as to leave the question of endocarditis in doubt. On the whole the cardiac signs of endocarditis are anything but a reliable indication as to the nature of the disease. Even in the case of extensive aortic involvement the only evidence of valvular abnormality may be a functional reflux in the mitral area.

Diagnosis in Acute Infectious Endocarditis

The diagnosis must be based on a consideration of the whole clinical phenomena associated in the case. As these vary from case to case the conclusion resolves itself into emphasizing the particular outstanding signs and symptoms. In one case it may be rigors and in another case it may be anemia, and in still another case it may be the emboli which find their seat in various parts of the body. Of great importance is the whole course of the case, due regard being paid to infectious incidents, such as puerperal states, pneumonia, or skin furuncle in the history of the subject. Indispensable to a thorough appreciation of the nature of the trouble is an accurate and repeated bacteriological examination of the blood.

Prognosis in Acute Infectious Endocarditis

The great majority of cases terminate after a longer or shorter period in death. Where the disease is a complication of acute septic infection, they run a course of two to four weeks, the issue being determined not exclusively by the cardiac complication, but by the toxic effects of the septicemia. Only a few cases terminate favorably and it is often the case that the valvular lesion can be determined only after the acute process has subsided.

Treatment of Acute Infectious Endocarditis

Treatment resolves itself into attempts to combat the general infection. In this respect due regard must be paid to the maintenance of nutrition by the provision of a copious, suitable and sustaining dietary. On no account, with the possible exception of digestive complication, should the patient be kept on a milk and fluid dietary. So far as possible, nitrogenous and carbohydrate foods should be given. Strong soups with rice and eggs, fresh meat, toasted bread, and fish should be provided. An attempt should be made to vary the dietary so as to make it appetizing to the patient. Care should be taken that there be sufficient sleep and rest, and camphor may be administered hypodermically with a view to the stimulation of the vasomotor apparatus. It is doubtful whether medicinal treatment is of much avail so far as the direct combating of the actual disease is concerned. Quinin, arsenic and iron may be helpful in their tonic effect on the nervous and digestive systems, and in helping the anemia which is almost invariably present. It is doubtful whether any of the specific anti-sera are of use, but for some reason or other anti-diphtheritic serum exercises a more profound effect on the human organism than any other anti-serum, such as anti-streptococcal serum or anti-gonococcal serum. This is not the occasion in which to enter into the properties of anti-diphtheritic serum as distinct from other anti-sera, but its obvious influence on certain kinds of non-diphtheritic inflammation of the throat and of gonococcal epididymitis proves that it possesses properties quite independent of those specific properties in virtue of which it is an indispensable adjunct in the treatment of diphtheria.

Nephritis, which is so frequently present, should be treated as part of the general process. There is no indication in this respect for diuretic treatment. In the case of those patients in whom the period of convalescence has supervened, the greatest care must be taken to provide rest for both body and mind. The general principle of a gradual return to mental and physical exercise must be kept in view. For a considerable period the strictest injunction must be made in regard to exercise and during this period every means must be adopted to nourish the body and stimulate the blood to a return to the healthy state.

Functional Disturbances of the Heart Following Infectious States

Emphasis has already been laid on the fact that it is impossible in every case to correlate circulatory disability with organic or degenerative change in the heart or peripheral circulation. Only passing reference may be made to this aspect of the subject here, in view of the fact that it is dealt with more fully in another part. We have dealt in the preceding paragraphs only with such infections as are frequently complicated by organic disease of the heart. Occasionally we find an acute myocarditis in typhoid resembling that found in diphtheria; myocarditis has also been described in scarlet fever, but these complications are so rare as not to merit especial attention. Pneumonia may be complicated, as we have seen, by septic endocarditis and this applies also to scarlet fever. But there is a class of circulatory disturbance characterized by a series of clinical phenomena common to a certain number of infections, a functional disorder of the circulation finding an expression in rapidity of the heart, palpitation, pain over the precordium, sleeplessness, restlessness, all of which symptoms taken together have been designated as "irritable heart" or "disorderly action of the heart". This condition will most frequently be found as a sequela of some infection such as influenza, trench fever, malaria, dysentery, etc., but it may also be present in nervous patients in whose history no trace of infection can be found. It should be emphasized that this syndrome is also found as an accompaniment of otherwise latent tuberculosis. Whatever its cause, or whatever may be the physiological sub-stratum on which it rests, it constitutes in many cases a very profound disability of the circulation. The part played by toxins and the part played by constitutional nervous instability, it may be difficult to define, but whatever the conditions of the occurrence of this syndrome it is essentially one in which the determining influence of infection must be taken into account.

CHAPTER XI

IRREGULAR ACTION OF THE HEART

By JOHN HAY

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Irregular action of the heart is a common phenomenon and its recognition by the patient or the doctor is not infrequently the cause of considerable apprehension, even in the absence of any evidence of cardiac failure. It is important, therefore, to be able to differentiate between those forms of irregular action which are of no moment and those which indicate serious changes.

In a normally acting heart there is a regular sequence of movements, a coordinated contraction of the various chambers followed by a pause during which the cardiac muscle recovers itself. At the termination of each systole all the functions of the myocardium with the exception of tonicity are in abeyance—the heart is in a refractory state. During diastole these functions are gradually restored, and by the time there is sufficient stimulus matter to excite the heart to another contraction, contractility and conductivity are again normal.

At the junction of the superior vena cava with the right auricle is a small mass of specialized tissue called the sino-auricular node. Here under normal conditions stimulus matter is produced and at regular intervals discharged; to this the muscle of the auricles responds. The contraction spreads over the auricles from this point and is conducted to the ventricles along the neuromuscular junction named the auriculoventricular, or A. V. bundle, and the ventricles in their turn contract. The rapidity with which stimulus matter is produced in the sino-auricular node is influenced materially by the vagus. The vagus acts as a constant curb.

The functions of the myocardium which more particularly concern us are *stimulus production*, most highly developed in the sino-auricular node or pacemaker, excitability, conductivity, and contractility. Abnormal or irregular action of the heart depends on the depression or exaltation of one or more of these functions.

When the manner of production of the various forms of irregularity is understood, there is usually little difficulty in recognizing the nature of irregular action when it presents itself. Occasionally, however, interpretation is difficult, and the use of the polygraph and electrocardiograph is necessary. I would like to emphasize, however, that the more familiar we become with variations from the normal rhythm the less often is instrumental help required, until finally a stage is reached in which it is possible, in almost every case, to arrive at a correct diagnosis by means of the unaided senses.

Classification of Cardiac Irregularities

It is usual to classify cardiac irregularity as follows:

1. *Sinus Arrhythmia.*—Here the irregularity originates at the sino-auricular node or normal pacemaker of the heart.
2. *Extra Systoles.*—The irregularity is due to premature beats originating either in the auricle or ventricle and independently of the fundamental rhythm of the normal pacemaker.
3. *Auricular Fibrillation.*—The sino-auricular node has ceased to control the heart. The auricles no longer contract in a coordinate manner. Instead, their muscle walls are in a condition of constant tremulous movement, without driving power, and the action of the ventricles is disorderly, powerful contractions and weak contractions occurring indiscriminately.
4. *Auricular Flutter.*—The auricle is contracting regularly at a very high frequency in response to a stimulus arising in some portion of its musculature other than the sino-auricular node. Often the ventricle responds to every second or third or even fourth beat of the auricle. In such cases the action is regular. With variations in the conducting power of the A. V. bundle irregularity in the action of the heart may ensue.
5. *Paroxysmal Tachycardia.*—Bursts of rapid action of the whole heart due to the excessive formation of stimuli in an abnormal site.
6. *Varying Degrees of Heart Block.*—The stimulus arising in the auricle is either delayed in its passage or occasionally fails to reach the ventricle which, failing to be stimulated, remains in diastole. If the block is complete the auricles and ventricles contract independently.
7. *Pulsus Alternans.*—Here, owing to defective contractility, every other beat is less powerful.

Of these seven groups the first and second are of common occurrence and minor significance. They must be clearly differentiated from all the other groups.

Certain other rare forms of irregular action occur, such as sino-auricular block, standstill of the whole heart in diseased conditions following the action of digitalis, the occasional independent ventricular systole under such conditions, and interpolated extra systoles, but the above seven groups include all cases of practical importance.

SINUS ARRHYTHMIA

The rate and rhythm of stimulus production in the sino-auricular node may vary, the variations depending on the tone of the vagus. These variations are often rhythmical, the rate rising and falling with the different phases of respiration. With inspiration there is a quickening of the rate, with expiration diastole is prolonged and the heart appears to lag. (Fig. 1.)

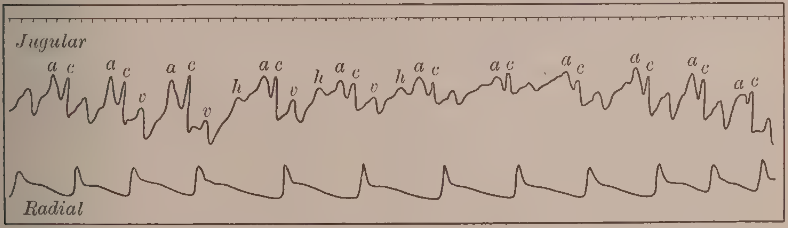

FIG. 1—POLYGRAPH RECORD SHOWING SINUS ARRHYTHMIA. The rate is quickened with inspiration and slowed during expiration.

a=Wave due to systole of the auricle.

c=Record of carotid pulse.

Such an irregularity is frequent in children and becomes more marked as the breathing is deepened. It is often very evident during the slowing of the heart in convalescence and must not be interpreted as evidence of something ominous. With more reason it may be viewed as evidence of a healthy myocardium.

Though sinus arrhythmia is commonly based on the respiratory phases, it does occur independently without any relationship to respiration, as a general temporary slowing of the heart with or without syncope. In some patients, at longer intervals, slight but definite slowing occurs, due to transient increase in the tone of the vagus.

There is little difficulty in recognizing this form of irregularity. Its existence must always be remembered more especially when examining the heart of a child or adolescent, and a clear relationship to the respiratory phases is decisive. With it the heart rate and the pulse rate are the same and no abnormal heart sounds are audible in the long pauses. When the heart is quickened from any cause, such as exercise, this irregularity disappears.

The discovery of sinus arrhythmia need cause no alarm. It is not evidence of disability. Variations in vagal tone are compatible with perfect health.

Treatment is obviously not called for.

Extra Systoles

Extra systoles or premature beats result from the existence of an irritable focus in some portion of the myocardium or junctional tissues where stimulus matter is rapidly built up and irregularly discharged. Such a focus is pathological and not physiological.

Extra systoles may occur at any age, but are much more common after middle age, especially when there are signs of arteriosclerosis. Those suffering from valvular disease also show an increased liability to this form of irregular action, and it should be remembered that it is much more common among patients who suffer from arterial or cardiac disease.

When a premature beat originates in the ventricle, the next normal stimulus on reaching it finds the ventricle either in a state of active contraction or in the refractory condition which is the necessary sequel to the just completed systole. Before the ventricle can contract again it must wait until the advent of the next normal stimulus; hence the post-extrasystolic delay or compensatory pause. (Fig. 2.)

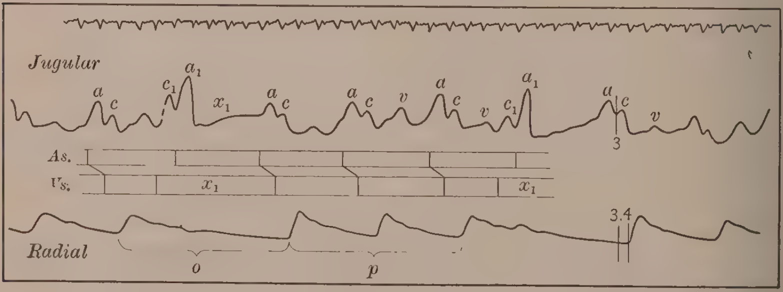

Fig. 2.—Polygraph Record Showing Extra Systoles Originating in the Ventricle.

a = Wave due to systole of the auricle. They occur regularly.
c = Record of carotid pulse and represents systoles of the ventricle.
c_1 = Premature appearance of carotid pulse. It anticipates the systole of the auricle a_1.
The compensatory pause is normal. $o = p$, each is 9½ fifths of a second.

This prolonged diastole, together with the preceding shortened diastole, equals in time two normal cardiac cycles. The compensatory pause is complete. When, however, the premature contraction is auricular in origin, we do not find the same complete compensatory pause. It is inadequate. (Fig. 3.)

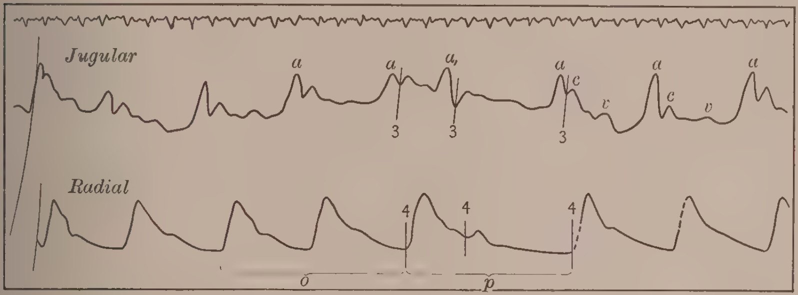

FIG. 3.—POLYGRAPH RECORD SHOWING EXTRA SYSTOLE ORIGINATING IN THE AURICLE TAKEN FROM PATIENT LIABLE TO PAROXYSMS OF AURICULAR FIBRILLATION.

a = Wave in jugular vein caused by systole of auricle.
a_1 = Wave in jugular vein caused by premature systole of the auricle.
c = Carotid pulse.
Note that the compensatory pause is incomplete. o is greater than p.

When the auricle contracts prematurely, its normal physiological impulse is anticipated and the fundamental heart rhythm is modified. In response to the premature systole of the auricle the ventricle contracts and the heart again lapses into its normal rhythm.

Patients may or may not be aware of the existence of these premature beats; if conscious of them they are frequently not at all inconvenienced or alarmed. Sometimes, however, the onset of recurrent extra systoles causes great anxiety and distress. This is more often so in the young, especially those with a high-strung nervous temperament. There may be transient sensations of giddiness, a fluttering of the heart, or a feeling as if the heart has stopped or rolled over; there may be some precordial pain. During the long compensatory pause, there is an uncanny sensation of emptiness in the chest, and the large forcible beat following this pause is felt as an unusual thud in the chest or neck, and often with each extra systole the patient gives a short gasp or cough. If they are numerous or occur at very short intervals the patient may feel ill, exhausted, or even collapsed.

On feeling the pulse of such a patient, the rhythm is regular, but at intervals a gap occurs in which no pulse can be perceived; this causes a temporary break in the sequence, or a small ineffectual beat is appreciated by the palpating finger occurring before it is due and followed by a compensatory pause. (Fig. 4.)

If the hand be placed over the cardiac thrust, the extra systole of the heart is felt as a sudden sharp jog, and the augmented force of the subsequent systole is perceived. Similarly, if the observer listens to the heart while his finger is on the radial artery, he will hear a rapid sequence of three or four sounds accompanying each intermission or premature beat. These sounds, on analysis, prove to be the first and second sounds of the normal heart beat preceding the extra systole, associated with the sounds produced by the extra systole. If the force of the extra systole is insufficient to open the aortic and pulmonary valves, then there is no second sound accompanying this beat and only three sounds are heard as at *x* in the diagram (Fig. 4), but if the extra systole is more forcible and blood is driven into the arteries, four sounds are audible, occurring in a group and followed by the long pause, as at *y* in Fig. 4.

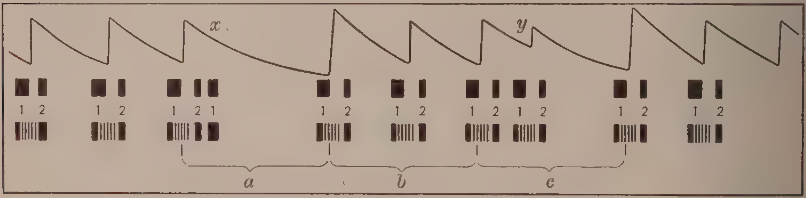

Fig. 4.—Diagram Showing the Effect of Ventricular Extra Systoles. At *x* there is an intermission of the pulse and a premature beat at *y*. The sounds of the heart are represented under the radial record and at a lower level a systolic murmur replaces the first sound except at *x* where the force of the ventricular systole was insufficient to produce a murmur. The compensatory pause is complete. $a = b = c$.

The existence of murmurs makes it a little more complicated, and it must be remembered that it does not follow that a premature beat will necessarily present the same murmurs as the preceding normal systoles. (Fig. 4.) The important thing is that auscultation reveals evidence of the contraction of the heart even when that contraction is so ineffectual that no pulse reaches the wrist. In an intermission caused by heart block, however, the ventricle does not contract and there is a long diastolic silence. There is the same silence in those cases of sinus arrhythmia which occasionally simulate the intermissions due to extra systoles.

Prognosis with Extra Systoles

The essential thing to remember is that, although extra systoles are in themselves of little importance, they are allied to and may be the precursors of a more serious form of cardiac irregularity, and in addition they indicate the possibility or probability of some diseased condition of the myocardium. When, therefore, extra systoles are present, the patient

Patent Foramen Ovale

The symptomatology of this condition is obscure, and, during life, its recognition is practically never possible. When it occurs alone it may give rise to neither symptoms nor physical signs, but cyanosis is sometimes present and murmurs of various kinds are often met with for which no other causes can be found. These are not only diastolic and presystolic, as might have been expected, but very frequently systolic in time. The area of their maximum intensity, also, varies in different cases; but they have generally been loudest over the third and fourth left costal cartilages. In rare instances in which a patient with this defect acquires mitral incompetence in later life, the defective state of his interauricular septum may be betrayed by the occurrence of a very marked venous pulsation in the neck without any evidence of tricuspid disease.

The prognosis in cases in which there is a large defect in the interauricular septum is obscure. Many of these cases die in early infancy; but not a few instances are on record of individuals with a severe degree of this lesion who have reached adult life and some even old age. It must, however, be remembered that the presence of a free opening between the auricles will constitute a danger to life should anything of the nature of venous thrombosis occur. A detached fragment of a thrombus carried to the right side of the heart is apt to pass directly into the left auricle and thence, through the left ventricle, into the arterial system causing embolism in the brain or elsewhere.

Defects in the Interventricular Septum

A persistent opening in the interventricular septum may give rise to no symptoms or physical signs; but in about half the cases in which it is the only lesion more or less cyanosis is present. In a smaller proportion —about a third— a systolic thrill is felt which may be confined to the base or felt all over the precordia. A harsh murmur over the third and fourth left spaces, well heard in the interscapular region behind, is present in most instances even when the opening in the septum is very small. It is usually systolic in time but it may be diastolic. The character of the murmur may vary considerably in different cases. A positive diagnosis of the defect is not possible.

The prognosis is on the whole less favorable than in cases of patent foramen ovale. It causes more interference with the circulation and leads to cardiac hypertrophy at an earlier stage. Cases have, however, been recorded in which patients with this lesion have lived from forty to forty-five years. The danger of the occurrence of embolism is the same as in cases of patent foramen ovale.

TREATMENT

Most children with congenital heart lesions require to be treated continuously as invalids; and a good deal may be done to prolong their lives and promote their comfort and happiness if their habits are so regulated as to prevent unnecessary exertion, excitement, all causes of chill and indigestion, which are apt to aggravate their symptoms. They should always have a period of rest in the middle of the day and their slightest ailments must be carefully treated on their first appearance. School life is generally out of the question for them. When anginal attacks occur, carminatives should be given after meals, and inhalation of amyl nitrite tried. If this fails to relieve their distress, as often happens, some form of opiate is indicated. In the cases in which there are signs of heart failure, epistaxis, and convulsions, digitalis is sometimes useful; but it has no effect on the cyanosis and other symptoms in most cases of congenital heart affection.

There are not a few children with loud murmurs from congenital heart disease who have no abnormal fatigue or discomfort on exertion and who require no special treatment, as they are practically in good health. These should certainly be allowed to run about freely and exert themselves reasonably in other ways as much as they like. Anesthetics and surgical operations are no more dangerous to them than to other children.

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CHAPTER XIII

CHRONIC DISEASES OF THE HEART

By SIR JAMES MACKENZIE

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INTRODUCTION

We are still so ignorant of the factors underlying the causation of heart disease, that it is impossible for a writer to describe the subject of this article in that simple and comprehensive manner which a full and complete knowledge of the subject would permit. A lack of knowledge of the cause of phenomena in nature compels a description of the manifestations as if they were distinct entities. This leads to a great accumulation of detail and renders a subject like disease of the heart confused and difficult of comprehension. If an earnest endeavor be made to understand the nature of the phenomena which disease produces, certain principles are revealed which admit of such an arrangement of the subject as enables the knowledge, limited though it be, to be used intelligently in the practice of medicine.

The origin and the insidious progress of heart disease are, in the majority of cases, hidden from us, and we are only brought face to face with heart disease after it has gone beyond the hope of cure, let alone prevention. The circumstance that brings a heart affection to light is generally some experience of the patient, some sensation of distress, which compels him to seek the doctor's advice. When the doctor examines the patient, he often finds the mischief already done, and all he can do is to guide the patient's future life in paths that will conserve the heart's strength. Fortunately, the detection of the trouble is often so early that, by giving sensible instruction, we are able to render valuable aid, not only in prolonging the patient's life, but in many instances in enabling the patient to lead a useful life and one free from suffering.

The means, by which this can be done, demand a thorough knowledge of the signs which the heart, in health and disease, can exhibit. The heart is an organ which gives excellent opporunity for its study. It is, however, played upon by so many influences that a knowledge is required of its behavior under a great variety of circumstances. There is, in many respects, a resemblance between the manifestations evoked by a healthy heart under certain influences, and those evoked by hearts affected by disease, so that it is necessary to have a clear conception of the nature of the symptoms, otherwise confusion arises and the practice of medicine is rendered haphazard and uncertain.

As disease or impairment of the heart is revealed by symptoms, in order to gain a means of estimating the significance of symptoms an orderly arrangement of symptoms based upon some clear principle is necessary. To that end I give at the outset a classification of symptoms which not only is based on sound physiological principles, but gives the doctor, who grasps the meaning of this classification, a guide in practice and research.

In the present state of knowledge of heart affections, it is impossible to give a complete picture of the diseases, but it is possible to describe essential matters which will be of the greatest value in recognizing the significance of the symptoms which we may detect. This is done by having a clear conception of the nature of the problem, *viz.*, the possibility of heart failure. The question in every case which confronts the doctor is, "is this heart failing," or "do these signs indicate the presence of heart failure," or "do they foreshadow its occurrence?"

The question of heart failure is, therefore, of the first importance, and before a doctor can, with assurance, treat or give an opinion as to the patient's condition, he must have a knowledge of what signs are evidence of heart failure. After dealing with the classification of symptoms, I shall discuss this question of heart failure. The conclusions drawn from this discussion reveal a simple method by which the heart's efficiency or the degree of heart failure can be estimated. Indeed, the method is so simple that many people do not realize that it is based on sound principles, and so, dissatisfied with it, seek after more tortuous and recondite methods. I, therefore, deal at length with the steps that were taken to bring to light the manner of perceiving heart failure as described here, so that the reader may appreciate, not only how heart failure may be discovered, but also the methods which clinical medicine requires for the solution of such problems.

As the manner in which the subject is dealt with is somewhat different from that usually pursued, inasmuch as it deals mainly with the detection of symptoms and the estimation of their significance in place of a description of the morbid conditions producing them—a description which lack of knowledge prevents my giving—I would respectfully request the reader to grasp fully the meaning of the first three subdivisions of this chapter (classification of symptoms, heart failure, normal and abnormal signs), as I have found that the knowledge which they contain tends greatly to simplify the practice of medicine, and affords a knowledge on which a reasonable prognosis and therapy can be based.

Classification of Symptoms

When we make an examination of an organ we are on the outlook for physical signs. We have been taught that in health the heart has a certain position in the body, a certain shape, that its rate and rhythm have certain characteristics, and that the sounds have certain peculiarities. Any departure from what has been recognized as normal is considered a physical sign of disease, produced by some structural change, so that we have a group of *structural symptoms*.

In an organ, like the heart, the question of its functional efficiency arises, and this is shown by the manner in which it maintains the circulation. The signs of an inefficient circulation are not shown by the heart, but by the manner in which the circulation is maintained in other organs, and there arises a series of symptoms indicative of heart failure, due to functional inefficiency; so we get a group of *functional symptoms*.

When the heart muscle is not supplied with sufficient blood or is itself the seat of disease or impairment, its forced activity gives rise to a set of symptoms, the outcome of muscle exhaustion, symptoms of suffering and distress, as pain, calling for a cessation of effort. These symptoms arise through a mechanism which involves the nervous system, so that there are produced certain symptoms, nervous in origin and protective in function; thus we get a group of *reflex symptoms*.

Symptoms, then, can be classified into three groups, structural, functional, and reflex. In addition there are secondary symptoms. As repeated references will be made to these groups, a short description is given here of their peculiar nature and significance.

Structural Symptoms.—It is necessary to hold clearly in mind what is revealed when we detect a physical sign, either by the unaided senses or by means of the many mechanical devices employed in their detection.

In the main, a physical sign implies an alteration in the structure of an organ, though this class includes also such signs as the modification of the sounds and movements of the heart. The detection of a physical sign gives little information beyond the fact that a change has taken place in the organ. There may arise from experience a knowledge that certain signs are associated with conditions of a definite nature bearing upon the health of the patient, as that an enlarged heart is often associated with heart failure, but heart failure is not revealed by a cardiac physical sign. It might seem to be a needless refinement to insist upon such a distinction, but for the purpose of keeping clearly in mind the limitations of knowledge revealed by a physical sign, such a distinction is necessary, for we find that in practice the detection of a physical sign is often thought to convey information far beyond what it actually reveals. Thus, for the last hundred years the detection of a murmur in the examination of the heart has led to the assumption that the heart was seriously affected, and today this view misleads the profession. Moreover, all the phenomena revealed by mechanical aids (by X-rays, by polygraphic and electrocardiographic records) belong to this group, as well as blood pressure findings.

The limited knowledge and the peculiar kind of knowledge revealed by a physical sign always must be kept in view, as the neglect of this has misled the profession in estimating the significance of symptoms in prognosis and treatment.

Functional Symptoms.—The essential matter in the maintenance of health is the functional efficiency of the organs of the body. A structural modification may take place and leave the efficiency unimpaired. Thus it arises that, after the detection of any physical sign, a careful inquiry must be made into the efficiency of the heart.

Functional symptoms are rarely detected from direct evidence in the heart, but rather from the effects produced on other organs. While the heart's condition and activity can be so easily studied, the information essential to a knowledge of its efficiency can only be made out by the reaction on other organs. As I have said, the study of the heart's various manifestations gives no idea of its functional efficiency, and this knowledge can only be acquired by observing how the circulation is maintained in other organs, as shown by dropsy or enlarged liver due to heart failure. Even in the slighter degrees of heart weakness the essential signs are brought about by a failure of the heart to supply sufficient blood to parts remote from the heart, as the center for respiration. The nature and significance of functional symptoms will be demonstrated in dealing with heart failure.

Reflex Symptoms.—There are a great many diseases in which we fail to detect any structural sign or any functional impairment, yet we can recognize the disease with great accuracy. The signs by which we are able to do this result from the irritation of a limited portion of the central nervous system by a peculiar form of stimulation produced by the diseased organ. Thus, in certain forms of appendicitis the only signs may be a sense of uneasiness or pain in the right iliac region, an excessive sensitiveness to pinching and pressure of the skin and deeper structures of the abdominal wall, and a rigidity of a portion of the muscle wall in this region. There also may be present a frequency of micturition. All these phenomena may speedily disappear after the removal of an inflamed appendix. In affections of the heart we may get a similar class of symptoms, as pain situated across the chest and in the arms, hyperalgesia of the skin and muscles in these regions.

When we group all these symptoms together we are driven to seek for a solution through the nervous system. Such symptoms as a hyperalgesia of the skin, with a contraction of the muscles, indicate the involvement of sensory and motor nerves supplied to the external body wall, and the stimulus producing them can only arise from some place where their nerve centers lie close together with the nerves from the heart. Such a center is found in the central nervous system.

In heart affections the nerves, supplying the skin and muscles of the affected region, have their cells of origin in the section of the spinal cord from which arise the seventh cervical and first, second, third and fourth dorsal nerves. From this region the sympathetic nerves supplying the heart arise. Therefore, we can say that the symptoms present in such a case are due to an irritability of the spinal cord—*an irritable focus of the spinal cord;* we find a group of symptoms produced by a reflex stimulation of the central nervous system, which affords a valuable aid in the recognition of the patient's complaint, and which will be described further on.

Secondary Symptoms.—Not only may the physical signs and symptoms of impaired functional efficiency and the reflex phenomena be manifested by diseases of the heart, but the heart may show symptoms as a reaction to the modified function of other organs. Probably the depraved function of every organ reacts upon the heart, either through the nervous mechanism of the heart, or from its nutrition being impaired. Infections may play upon the heart either from the direct effect of the microbes or from their toxins.

The recognition of a class of symptoms, which are secondary and due to the functional disturbances of other organs or to infection, is necessary because it gives a line of investigation in each case. Already we know of many symptoms produced by different organs, which are associated in their appearance, and we recognize certain groups of symptoms as due to the altered or impaired function of an organ, so that the appearance of one of a group leads to a search for others.

This matter is of importance from the standpoint of treatment. It is manifest, if the heart is disturbed by the depraved functions of other organs, how useless any treatment will be which is devoted to the heart. Yet this view needs emphasizing, for, to my knowledge, large numbers of individuals are submitted to prolonged treatment for cardiac symptoms in which that organ is only secondarily affected. Indeed, so important is this aspect of the matter that the question should arise in every case whether the symptoms are not provoked by some other organ, or by some general disease in which the cardiac manifestations are but a part.

The Significance of Symptoms

The importance of the classification of symptoms, just given, will be realized by demonstrating its practical application. When a patient consults a doctor it is because he is not feeling well. A doctor, in his examination of the patient, in addition to hearing the patient's account of his trouble, may detect some physical sign. There is a tendency to associate the sensations of ill health with the presence of the abnormal sign. This is apt to occur with an abnormal cardiac sign, for in practice we find many people who have been warned of some obscure danger because their doctors had detected a murmur, or an irregular action of the heart, or an increase in the blood pressure. Many of these warnings are quite unnecessary, and have arisen because there exists a great defect in medical knowledge. This defect consists in a lack of knowledge of the significance of symptoms.

When a doctor detects an abnormal sign in his patient, the mere detection of the sign is but a preliminary step in his examination. There is much more required of him. The patient expects that he will be able to tell how that sign came to be there, and to foretell what will happen if the cause producing the sign is left untreated. The doctor is also expected to know if the cause is amenable to treatment, and what is the appropriate treatment.

This kind of knowledge, commonly included in the term "prognosis," has not received that attention which it deserves. The need for this knowledge meets the practicing doctor in the examination of every patient, and is so essential to him in his work that it might have been supposed it would have called for a thorough investigation. Strange as it may seem, no subject in medicine of equal importance has been studied so imperfectly and inefficiently. It is tacitly assumed that it is a subject easy of understanding and needing no particular training for its pursuit. Nothing could be further from the truth, for it is a subject that requires for its pursuit a very profound knowledge of the manifestations of disease. It can truly be said that its importance has never been fully recognized, nor has it been realized how essential it is to the intelligent practice of medicine. So little has the subject been appreciated that it has not even been understood how a knowledge of the subject can be acquired.

The basis for a knowledge of this kind requires a recognition of all the manifestations of disease, so that they can be clearly differentiated the one from the other, not only in regard to the mechanism of production, but as to the bearing the cause of each symptom has on the patient's future. To accomplish this, all the usual methods of clinical examination are necessary, but carried out with a clearness of purpose that has been wanting in a great measure. It is manifest that the significance of an abnormal sign can only be found by watching individuals who manifest it during the period of life when it is present. As the abnormal sign may be present for long periods of years, the observer must have the opportunity of being in contact with the affected individual for a long time. The vast majority of signs can only be assessed properly when consideration is given to the presence or absence of associated phenomena; therefore, in addition to watching individuals who present an abnormal sign, it is necessary that the observer should be on the outlook for other signs. The nature of these other signs and the manner of searching for them will be understood if the significance of the classification just given be fully grasped. On the detection of a structual or physical sign, the functional efficiency of the heart must be inquired into. The recognition of this necessity will direct attention to the kind of evidence required to complete the examination of the patient. The manner in which the knowledge for assessing the value of cardiac signs can be acquired will be shown under the next heading.

Heart Failure

The impaired health, that results from a weakness of the heart, and the danger to life, that frequently occurs in disease of the heart, have surrounded all questions associated with the heart with an atmosphere of dread. The medical profession are ever inventing new ways for studying cardiac disturbances. The result of this study has been to employ numerous methods for the detection of signs that might give warning of impending danger. As the source of danger has been imperfectly realized, new methods are being continually invented in the hope that new light might be thrown upon the matter, but on account of the lack of understanding of the manner in which heart failure is brought about, such investigations are haphazard and result in the employment of methods unsuited for the purpose, and in the accumulation of details that obscure the issue. It is necessary to have a clear idea of what heart failure is and how it is brought about, and for that purpose I deal here with the subject in some detail, in order to show that the principles underlying the production of heart failure are of simple kind, and that, when they are understood, the recognition of heart affections becomes comparatively easy, while treatment is rendered rational and effective.

The Importance of the Heart Muscle in Maintaining an Effective Circulation.—The purpose of the circulation is the supply of a constant stream of material, capable of nourishing the tissues, and the removal of such waste products as are capable of entering the circulatory channels. As a continuous pressure is required to force the blood onwards, the intermittent pressure, conveyed to the blood stream by the heart, is converted by the resiliency of the arterial walls into a constant pressure at the periphery of the arterial system. The maintenance of the arterial pressure is the outcome of the force exerted by the ventricles and of the resistance of the smaller arteries and capillaries. The full force of the ventricular contraction is not spent on the blood current merely during the period of systole. In throwing the blood into the arterial system, ventricular contraction does so with such force that it distends to a slight extent the larger arteries. The elastic coats of the arteries, as soon as the ventricular systole is over, compress the column of blood within them, and in this manner maintain a degree of arterial pressure during the period that the ventricle is not acting. The ventricular force is thus stored up by the distension of the elastic coats of the arteries and liberated during ventricular diastole.

The heart muscle supplies the force which maintains the circulation, while the various parts of the mechanism of the circulation are so adjusted that all parts combine to facilitate the work of the heart and to attain the object of the circulation. A disturbance of that adjustment interferes with this mechanism and throws more work upon the heart muscle. So long as the heart can overcome the impediment and maintain the circulation in a normal manner, no symptoms are evoked, but if the heart muscle is embarrassed and is no longer able to carry on the circulation efficiently, then certain phenomena arise at once, and these phenomena we call "symptoms of heart failure."

From this consideration it will be realized that *heart failure is simply an inability of the heart muscle to maintain an efficient circulation*, and that this failure of the heart muscle is due to the muscle having some impediment embarrassing it in its work, or to some defect in the muscle itself. This failure may arise from exhaustion when the circulatory organs are healthy, or from a disturbance of the normal adjustment of the various factors concerned in the circulation. This disturbance, in fact, may arise in a great many ways, but the final result is the same, that is to say, embarrassment of the heart muscle and its final exhaustion.

The Rest and Reserve Forces of the Heart Muscle.—In order that the essential signs of heart failure may be recognized and the mechanism of their production understood, a study of the heart both with the body at rest and during effort gives the means for acquiring this necessary knowledge. As the heart possesses the power, not only of maintaining an efficient circulation when the body is at rest but of varying its activity according to the bodily requirements, the force inherent in the heart muscle may be considered, for practical purposes, to be composed of two parts; that is to say, a part which is employed to maintain an efficient circulation when the body is at rest and which therefore may be called the "rest force," and a part which is called into action when effort is made and which may be termed the "reserve force." The rest force is the minimal force which the heart has to exert to maintain the circulation at a level consistent with life. The impairment of this rest force produces those evidences of heart failure which persist when the body is at rest, such as dropsy and dyspnea. The continuance of such impairment eventually leads to a fatal issue.

The second part of the heart's force (reserve force) is that which is called upon when the body makes some effort. While the body is at rest, this potential force is not exercised, but its possession enables us to undertake with ease all forms of effort. Inasmuch as this part of the heart's force is only used when exertion is made, it may appropriately be called the "reserve force" of the heart.

The Beginning of Heart Failure.—Heart failure is shown first by a limitation of the reserve force. An individual becomes conscious of this limitation by finding that some form of exertion, which he was used to perform with ease, now causes distress. Heart failure invariably starts, in the first instance, by exhaustion of the reserve force. The exhaustion is slight at first, but by the persistence of the causal factors it proceeds apace, until after a period, long or short, this exhaustion induces such distress as to compel attention, or the rest force is encroached upon, and with the exhaustion of the rest force a point of danger to the life of the individual is reached.

When a healthy individual undertakes some form of severe bodily exertion—for example, running at the "top of his speed"—there comes a time, sooner or later, when he suffers a temporary exhaustion of his reserve force. Ultimately, on account of this temporary exhaustion, he is compelled to desist. If he attempts to run again before he has a period of rest sufficient for the restoration of the muscle he will not be able to maintain his full speed during so long a period as in the first instance. If he systematically denies himself a sufficient period of rest his powers of endurance will gradually become more and more restricted. This, which we recognize as natural in a healthy individual, is identical with the process occurring in an individual having some cardiac defect, whether the defect is due to disease of the heart itself or to other factors which embarrass the heart in its work.

It will be seen, therefore, that exhaustion of the reserve force in individuals with enfeebled hearts is of the same nature as exhaustion of the healthy heart, and that heart failure in the first instance is simply the premature exhaustion of the reserve force of the heart. No doubt exhaustion in diseased hearts can be brought about in a greater variety of ways than exhaustion in healthy hearts, but this consideration is not germane to the point at issue. Whether it is an affection of the heart muscle, which tends to induce the exhaustion, or the irregular action of the different parts of the heart, or the too great frequency of the rate of contraction, or a valvular lesion, the result is always the same and the laws governing the production of the symptoms are the same. The only difference between a man in fair health and a man with an affection of the heart which limits his efforts is that, in the case of the latter, certain disagreeable sensations are provoked more readily than in the case of the former. The sensations are identical in kind. Any modifications they may show in different states of health are quantitative only. The patient with a heart affection no doubt tends to suffer a greater degree of exhaustion than the man possessed of a healthy heart, but the mechanism by which the sensations are produced is identical.

It is evident that, if the "rest force" is intact, the individual, when at rest, will present no signs of heart failure. It is also evident that in the early stages of heart failure the signs of exhaustion will only be found when an effort has been made, as it is only then that the limitations can appear. That there is a limitation can be known in the very early stages only to the individual affected. In other words, the evidence of heart failure in the early stages is entirely subjective; the individual becomes conscious of certain sensations of distress or discomfort on making an effort which, before this time, he was able to make without experiencing these sensations. As the heart failure advances, these sensations are provoked by less effort, until finally the "rest force" becomes encroached upon; then we get objective evidences such as dropsy and labored breathing while at rest.

Conditions That Induce Heart Failure.—I have already remarked that, in the normal condition, the adjustment of all parts concerned in carrying on the circulation is essential to efficiency, and that any disturbance of the adjustment at once calls for an increased effort on the part of the heart muscle. Such calls are made first on the reserve force and, if persisted in, lead sooner or later to its exhaustion. The causes are extraordinarily varied in character, and may arise from a disturbance of any of the factors on which the normal circulation depends. It is from this standpoint that diseases of the heart should be considered, inasmuch as it is only by looking at the matter in this light that a proper perspective is obtained in regard to the significance of any abnormality. Thus irregular action of the heart should be described from the point of view of its effect upon the efficient performance of the heart, as well as the condition producing it. Valvular defects should be studied, not as specific affections to be considered in themselves, but rather as a source of embarrassment to the heart muscle in its work, or as indicating the presence of a lesion that may have extended to the muscular wall. In the same manner arterial degeneration and high blood pressure should be considered as conditions which upset the normal adjustment of the factors which carry on the circulation. Inherent defects of the muscular wall itself should be viewed in relation to their bearing on the heart's efficiency.

To appreciate the meaning of heart failure, we must, as has been indicated, bear in mind that the force maintaining the circulation is the heart muscle. There is a limit to the amount of work which a healthy heart muscle can perform. It is the forcing of the heart to work beyond this limit that produces heart failure. We are justified, therefore, in looking upon heart failure as the expression of an exhausted heart muscle.

It will be clear from the foregoing that the sensations produced by exhaustion of the heart muscle, however easily provoked they may be, give no clue to the underlying morbid condition. This fact must be borne in mind. The actual morbid condition present must be determined by the consideration of other evidence revealed by the history and by the physical examination. The sensations, however much they may vary in degree, are common to all forms of heart impairment. The well-known fact that certain sensations are apt to occur more readily with some affections than with others, as for example pain in aortic disease, in no sense alters this fundamental truth.

The Functional Efficiency of the Heart

On account of its accessibility to examination, and the ease with which its activities can be studied, the heart is a very suitable organ for the purpose of studying its functional efficiency. In a manner this has been done from time immemorial, for the taking of the pulse has that object in view. But though the importance of the subject may have been realized, and many attempts made, both by clinicians and physiologists, to find out, like much else in medicine, it was not understood how the inquiry should be pursued Attempts have been made to acquire the knowledge by experiments on animals, and the introduction of every new instrument during the last hundred years, from the introduction of the stethoscope to the latest laboratory contrivance, has arisen from an attempt to solve the problem.

The failure of these attempts was due to the fact that the only way this object could be achieved was not understood. The recognition of impaired efficiency can be attained only by using those methods that are peculiar to clinical medicine, *i.e.* the careful differentiation of symptoms with an appreciation of their significance and the watching of individual cases with varying degrees of impairment for a sufficient length of time. Hitherto attempts to find out the functional efficiency of the heart have depended mainly on the study of physical signs, as by carefully noting the character of the sounds of the heart and the various murmurs, and how they were affected by effort; by the counting of the heart beats or taking the blood pressure before and after effort; or by means of registering the movements of the heart by sphygmograph, polygraph, and electrocardiograph. As these methods discover only symptoms belonging to the structural group of the classification of symptoms, they do not reveal the symptoms essential to the understanding of the functional efficiency of the heart.

Symptoms Which Reveal the Functional Inefficiency of the Heart

As I have already pointed out, in all hearts there is a reserve of strength only called upon by effort, and the first sign of the heart's strength being impaired is shown by a premature exhaustion of this reserve force. Attempts to acquire a knowledge of this limitation from mechanical devices or laboratory methods have failed. If, however, we study the sensations produced by effort when pushed to the point of exhaustion on all sorts and conditions of people, we observe that there speedily are produced certain phenomena which give the desired information.

At first sight the sensations produced by a failing heart seem so indefinite that no clear conception of their nature or mode of production can be acquired. However, a persistent attempt should be made to have each sensation clearly differentiated. Distressful sensations arise when effort is made beyond a certain limit in people with healthy hearts as well as in people with damaged hearts. In people with healthy hearts the distressful sensation is one of breathlessness as a rule, though in a few people there is a sense of constriction across the chest which almost amounts to pain. When from any cause gradual heart failure sets in, the symptoms are the same but produced by a slighter effort. This is best seen in people getting on in years, in whom nothing can be detected amiss with the heart, and the only evidence of impairment is a limitation of the field of response to effort.

While breathlessness, occurring after an amount of exertion that the individual was wont to undertake with comfort, is the most common sign, in some tightness and oppression across the chest are the chief signs provoked, accompanied in some people by pain which, in a few, becomes so severe as to present the symptoms which are recognized as angina pectoris.

These two kinds of sensation are those which give the truest estimate of the heart's efficiency. The one, breathlessness, belongs to the functional group of symptoms and arises from the heart failing to supply the center of respiration in the brain with sufficient blood. The other, pain and oppression in the chest, from the reflex stimulation of motor and sensory nerve centers in the spinal cord provoked by exhaustion of the heart muscle, belongs to the reflex group of symptoms. This distinction between the signs of functional inefficiency (breathlessness) and of a pure cardiac reflex (pain and oppression) is based on the study of certain peculiar morbid conditions.

Breathlessness.—When breathlessness arises from cardiac inefficiency it is always found to be associated with a diminished output of blood, or rather, an output insufficient to supply the respiratory center. Physical effort, under normal circumstances, calls for an increased supply of blood to the active parts. This is met by an increase in rate of the heart beat and a dilatation of the vessels supplying the active parts. It is unnecessary to dwell upon the fact that there is a limit, even in health, to the response of the heart to effort, that limit being shown by the distress in breathing.

This sign of cardiac inefficiency can be demonstrated, by the story of certain morbid states, to be due to the deficient supply of blood. In most cases of auricular fibrillation the response to effort is accompanied by such an increase of rate that many of the beats are so ineffective that little or no blood may reach the periphery, and breathlessness is the most clamant symptom in the majority of these cases.

As an increased output from the heart is required to supply the active muscles during exertion, to meet this demand the heart's rate has to increase. In certain diseases the ventricular rate does not increase in response to effort, and as a result, breathlessness is induced with other signs, due to a lack of blood supply. In complete heart block the rate of the ventricular beat is steadily about thirty per minute, and it does not increase in response to effort. When individuals with such an affection hurry in their walk, or attempt to run, most of them are pulled up by breathlessness. A few may feel other sensations, as a swaying feeling as if they would fall, or their feet feel heavy as if loaded. These sensations manifestly are due to a deficient supply of blood to the brain and feet. Another instance where the heart's rate is uninfluenced by effort is in auricular flutter. Here the auricles usually beat about 300 per minute, and the ventricles respond in many cases only to every second beat, the ventricular rate being about 150. Effort has no effect, as a rule, on either auricular or ventricular rate, but it provokes the sensation of breathlessness and not of pain.

From these observations it is seen if, in response to effort, the output of the heart is diminished or not increased, breathlessness is readily induced.

Pain.—The reason for stating pain as an expression of exhaustion of the heart muscle arises from the consideration already given of the reflex group in the classification of symptoms. In the study of cases of angina pectoris it was frequently found post-mortem that the coronary arteries were so extensively diseased that for many years the heart could not have received a sufficient supply of blood to enable it to function efficiently. Moreover, a consideration of what happens to any muscle, when forced to work with an insufficient supply of blood, affords confirmatory evidence. Thus in cases with degeneration of the arteries of the leg, leading ultimately to gangrene, the patients for a long time may be unable to walk more than a few hundred yards, because they are pulled up by pain in the legs and feet. In a patient, in whom the femoral artery had been blocked, effort beyond a limited extent resulted in pain in the legs of such an agonizing kind that he was compelled to stop. In many people, in whom the heart is not affected with actual disease but the muscle is weakened from other causes which have impaired the health, as toxic affections elsewhere, anemia or impaired nutrition, with overwork, pain is a frequent symptom. Accompanying the pain, particularly in this latter type, there is often hyperalgesia of the skin of the left chest, especially under the breast.

The pain and hyperalgesia are always present in the field of peripheral distribution of the sensory nerves, whose centers are associated in the spinal cord with the centers of the cardiac sympathetic nerves. This field of distribution is shown in Fig. 3, page 425. Sometimes the pain is felt along the jaw or in the neck, in the peripheral distribution of sensory nerves associated in their origin with that of the vagus. These people, when effort is made, are frequently pulled up by the pain, and when sufficient rest is not obtained the tendency to pain becomes much increased, while the area of cutaneous hyperalgesia enlarges.

The Sense of Exhaustion.—In the systematic inquiry into the nature of the sensations produced by effort, other sensations were recognized, the most frequent being a sense of exhaustion or fatigue. Although not a cardiac sensation, it is so intimately connected with the circulatory system that it needs to be considered. This sensation causes a great desire to sit or lie down. In many cases it speedily passes off when this can be done. If forced to carry on, some people become faint and lose consciousness.

There are many varieties of this sensation produced in different ways besides effort, as in standing in a hot room. It is assumed in many cases to be cardiac in origin, but it seems to be due to some vasomotor disturbance inducing a cerebral anemia, the result of a dilatation of the peripheral vessels with accumulation of blood in them, such as in the large abdominal veins or the vessels of the skin, especially when the body is rendered warm by exertion and heavy clothing. As many of the people who suffer from this are debilitated from other affections, the heart is often weak from the same causes, but the sensation is not, as I have said, properly speaking, a cardiac one. This matter will be more fully discussed later on.

ESTIMATION OF THE AMOUNT OF RESERVE FORCE

I have endeavored to find some standard by which the amount of reserve force and its exhaustion could be expressed in terms of precision. I have, however, failed to find any definite standard, and when one reflects, it will be realized that it is not possible that a measure of such definite precision, as to be applicable to all cases, should be attainable. Since the ability to undertake effort is due to the possession of a reserve force, we recognize that, in healthy people, the amount of reserve force is subject to great variations. Among trained athletes there are some capable of much greater endurance than others, and the terms "short-winded" and "long-winded" imply really different amounts of reserve force. The term "training" used in athletics implies, amongst other things, the aquisition of an increased amount of reserve force. This is due to the power possessed by the heart of increasing the efficiency of its functions by their systematic and judicious exercise. Conversely, the neglect to exercise the reserve force leads to a diminution of its amount, as witnessed in the speedy exhaustion of healthy people who lead sedentary lives. This latter fact is of importance when the amount of reserve force is limited in people who may present some abnormal cardiac condition. In such people the limitation of the field of cardiac response may be due to the lack of exercise of the reserve force.

The standard, therefore, by which we can estimate the amount of the reserve force is in the main personal, each individual unconsciously acquiring the knowledge of what he can do. So long as he exercises the heart within the limits of his powers, no symptoms arise, but as soon as the reserve force is exhausted and the effort is persisted in distress and discomfort are experienced. Thus it will be seen that the evidence of exhaustion is common to sound and impaired hearts, varying only in the ease with which it is provoked. The chief requisite in estimating the degree of inefficiency of the heart is thus an experienced physician with a knowledge of the significance of symptoms.

ONSET OF HEART FAILURE WITH PATIENTS IN BED

Patients who are confined to bed from illnesses other than the heart may develop heart failure, as old people who have to lie in bed because of a broken leg; or others who suffer from an exhausting illness, as typhoid fever; or a pregnant woman. Naturally, in these no test can be applied, nor does reference to their past experiences give much help.

If we watch carefully we may find certain early signs which will put us on the alert. A slight increase in pulse rate and a slight increase in the rate of breathing should always arouse suspicion. The increased rate in breathing may not be noticed unless looked for; it is generally quiet and shallow, and when counted it will be found over twenty per minute. An examination will reveal in many such cases crepitations at the base of the lungs. In these cases the examination should begin by asking the patient on which side he lies; then make him sit up, and auscultate the base of that lung on the side on which he had lain, and at the same time ask the patient to take in one full and deep inspiration. This opens up the alveoli at the base, and if there is any abnormal moisture it is manifested by numerous fine crepitations. Healthy people show no sign of this. Slightly weakened hearts may show it with the first deep inspiration only; if there is distinct cardiac enfeeblement, the crepitations do not disappear. I have seen cases where the first sign was the crepitation during the first deep inspiration, and gradually the crepitation became more persistent until the resonance of the bases of the lung became impaired, even to complete dullness with no breath sounds, and at the post-mortem examination the lungs at the bases have been sodden and airless. In some instances, there have been patches of inflammation (catarrhal pneumonia—the hypostatic pneumonia of the feeble). I have also seen this hypostatic congestion disappear, and as the patient improved, the crepitations gradually disappeared, the last sign being the crepitations with the first deep inspiration.

I have found this method of observation of the greatest practical use. In the elderly it governs the position which the patient should occupy—lying down or propped up. In typhoid fever it is a prognostic sign of the very greatest value—the absence of edema of the lungs indicating that the heart has escaped, while its presence and gradual increase is a sign of great gravity. In heart disease it is likewise one indication of the heart's condition and in the complication of pregnancy and heart disease it is one of the most important guides in the management of these cases.

It is of no less importance in treatment, as will be realized when the reason for its appearance is appreciated. It invariably accompanies dilatation of the right heart, and the manner of its production seems to be as follows: The factors that move the blood through the lungs are twofold; first and most important, the right ventricle; and second, respiration. In healthy hearts, the first of these is so powerful that the second is scarcely appreciated. When, however, the right ventricle is enfeebled, the assistance of the respiratory movements becomes necessary. When the patient lies in bed on one side, the pressure of the ribs on the mattress restrains their movements, so that the flow of blood through this part of the lung is retarded and edema results. This can be shown in the early stages, for when the patient breathes deeply, the whole of the crepitations may disappear.

SUMMARY

By following a line of observation, in which the physical signs and the sensations evoked in response to effort were carefully noted in individuals leading strenuous lives, many showing a progressive weakness of the heart, all phases of heart failure, with the accompanying phenomena, were observed; and in many who died, by obtaining a post-mortem examination and having the heart examined by skilled pathologists, certain deductions were drawn, of a simple kind, which became of the greatest service when applied in practice. Briefly these were:

The heart's efficiency can be perceived by recognizing the manner in which it responds to effort.

The first sign of heart failure is shown by a sensation of distress in the individual undertaking some effort he was accustomed to perform in comfort. The amount of effort undertaken without distress gives the measure of the heart's functional efficiency.

The chief sensations of distress produced by the exhaustion of the heart are breathlessness or a sense of constriction across the chest or pain.

These propositions have reference to individuals able to be up and about. The signs of heart failure occurring in individuals, when confined to bed, have been described. Extreme forms of heart failure will be described in discussing affections of the myocardium.

The Nature of Cardiac Symptoms

Normal and Abnormal Signs.—Most organs of the body present certain evidences by which we recognize their presence, and experience shows that these evidences are fairly constant and reliable, so that certain signs are recognized as normal. Departure from normal characteristics is looked upon as possibly indicating the presence of disease, though it is well recognized that most organs may show certain modifications, which are unusual but nevertheless quite consistent with health. Perhaps no organ can show so many variations in its manifestations in health and disease as the heart. Not only are the normal variations bewildering in their number, but these are so like the manifestations of disease that the utmost confusion prevails as to the meaning of many very obvious signs. It is necessary, therefore, to consider the variations that are consistent with health, and to find some means by which the significance of doubtful symptoms may be determined.

To a certain extent this has been shown by the steps which were taken to assess the functional efficiency of the heart. But this wants a little more elaboration, as the signs which, in one person, may be quite normal, in another person, may be signs indicating a certain degree of heart failure.

Normal Limitations of the Heart's Response to Effort

I pointed out that the first sign of heart failure was a limitation of the individual's power to respond to effort as shown by the appearance of certain distressful sensations. There are a great many healthy people who are normally short-winded, and who are never able to run far or walk up a hill rapidly without being pulled up by distressful sensations. This limitation is quite normal to them, though in another individual such a limitation would indicate serious trouble. To recognize the difference it is necessary to find out the amount of effort the individual was able to perform at such time as he considered himself to be in fair health, and it will be found that, in the normal individual, there was always present this limitation, while in the impaired individual, the limitation had come on and progressed in a definite manner from the time when he was able to take such effort in comfort.

Normal Variation in Heart Rate.—There are great varieties in rate amongst healthy people. In children, up to ten years of age, the rate in the healthy may vary from 120 to 80 and even less. In the young adult the variation may be from 100 to between 50 and 60. In adults the variation may be from about 90 to 50 or even a little under. The slowest normal acting heart in a healthy man, that I have seen, was a little under 30 beats per minute. With this one exception every case I have observed, with a rate under 40, suffered from heart block, the result of disease or from an excessive use of digitalis.

Normal hearts respond to effort or fever by an increase in rate. Damaged hearts also, as a rule, respond by a much greater increase in rate than normal hearts, but the variations are so great that little reliance can be placed upon any degree of increase as a sign of heart efficiency. Even in healthy men in good training the rate may become very great after effort, reaching sometimes to 200 beats per minute. Even the time taken for a heart's rate to fall after cessation of effort is so variable in health, as well as in disease, that no useful criterion can be obtained from this kind of observation.

Normal Variation in Size and Shape of the Heart.—The size and shape of the heart may also show considerable variation within normal limits. In children the heart is higher up in the chest than in adults, so that the apex beat is not infrequently found in the fourth interspace, half an inch or even an inch outside the nipple line. This high position may be due to the greater relative size of the liver raising the diaphragm, or it may be due to the fact that the relation of the heart to the chest wall alters as time goes on. The variation of the position and shape of the heart, revealed by percussion and the X-ray, is due to the different shapes of the chest and the varying height of the diaphragm. One finds in some healthy people the apex beat in the sixth interspace and in others in the fourth. In the female the heart is slightly smaller than in the male.

Normal Variations in the Sounds of the Heart.—When we consider the factors concerned in the production of the sounds of the heart, the taut stretching of the membranes held in position by bands partly muscular and partly tendinous, the contraction of the muscle of the heart, the variation in the amount of the muscle, the varying contents in the cardiac cavities and other incalculable factors, we need not be surprised when in practice we find a great variety in the modifications of the sounds of the heart in people enjoying robust health. The deductions to be drawn from murmurs will be described in the chapter on murmurs; here I merely wish it to be recognized that there are no grounds for supporting the view that the efficiency of the heart can be inferred from any peculiar character of the sounds. When some modified sound is associated with heart failure, there will always be other more reliable signs, while to base an opinion on a modified heart sound is sure to lead the observer astray.

Variations in the Heart with Age.—There is another matter which should always be kept in mind in dealing with the cardiac phenomena, and that is the influence of age or rather of the changes brought about by the different periods of life. Some of these will be referred to in dealing with special phenomena, such as irregular action of the heart and murmurs, but it is well to recognize that the modifications of the heart's action may produce signs, undoubtedly pathological, but of such slight significance that one may consider them as normal to the period of life in which they appear. We all recognize in the face certain lines and wrinkles which we look upon as signs of advancing years, but do not consider them pathological. The graying of the hair, the thinning of the skin, are evidences of advancing years. Such changes which are evident in the external parts of the body have associated with them changes of a similar nature going on in the internal organs. These are most evident in the heart, so that from infancy to old age in the healthy and vigorous, as well as in the frail, changes occur, which may be of little moment, but which give rise to symptoms which may easily mislead the unwary. It is incumbent then, when the doctor discovers any sign which he takes to be abnormal, to ask first whether the sign may not be, after all, a physiological manifestation, or be the outcome of some slight change in the heart which is due to the changes associated with advancing years, and therefore is of little importance.

These changes, signs of advancing years, are most of them due to a deficient supply of blood to some particular tissue.[1] Thus the thinning of the skin, which makes such a difference between the thick skin of the child and the tissue-paper-like skin of the old, is mainly or entirely due to a difference in the number of capillaries. In the heart the fine texture of the valves is normally supplied with only a small quantity of blood, and with advancing years the supply diminishes with a consequent thickening and retraction of the fine edges of the valves. The consequence of this is a modification of the sounds of the heart, producing muffled sounds and murmurs. These changes seldom reach a degree which embarrasses the heart muscle in its work, and though the noise which they make may seem alarming in its loudness, yet they are free from danger. Similar changes in other parts of the heart may produce equally innocent signs, such as irregularities, chiefly of the extra-systole kind, and occasionally slight changes in the auriculo-ventricular bundle, producing a slight degree of heart block.

The limitation of the heart's power to respond to effort occurring in advancing years has a variety of significance, and the rate at which it advances and the extent it has reached have to be carefully weighed in a common-sense manner to find out whether it is only such as one would expect at the period of life the patient has reached, or whether it is proceeding at such a rate as to raise the suspicion that some disease process is present more active than the senile changes would account for.

Variations in the Female Heart.—In women during menstruation, pregnancy, and the puerperium and lactation there are changes, more or less marked, which should always be reckoned with in estimating the significance of any cardiac sign. The most common changes are alterations in the sounds. Systolic murmurs come and go in a somewhat bewildering fashion during pregnancy and the puerperium. The heart is said to be increased in size during pregnancy, but this is far from being settled. The increase of the uterine tumor presses up the diaphragm and induces a displacement of the heart so that the apex beat may be found in the fourth space and well outside the nipple line. Such a displacement may modify the sounds so that systolic murmurs may be produced. But it is difficult to say how they are produced, and it would not be profitable to discuss them, as we are so ignorant of the factors concerned in their production, and my purpose in referring to them here is to insist that no grave significance should be attached to symptoms developed or detected at those times without due consideration being given to the possibility of their being but incidental changes of no significance.

With the onset of the menopause, it is well known that many phenomena, mostly of a nervous character, appear. In many women at this time cardiovascular symptoms are frequent. They are mostly of a vasomotor kind, flushing, exhaustion, and irritability of the heart being the most common. Attacks of cardiac pain, sometimes of great severity and resembling in some respects those due to serious disease of the heart are not uncommon. With these I deal in the chapter on angina pectoris, as well as with the areas of hyperalgesia in the left chest, which are apt to appear in women at this period of their lives.

Response of the Heart in Affections of Other Organs

Further it must be borne in mind that the heart is extremely sensitive to stimulation from outside sources. It is possible that derangement in the function of every organ in the body stimulates the heart either reflexly or from the effect of the deranged function acting directly on the heart or its nervous mechanism. This should lead to the scrutiny of the whole individual in every case where the heart is suspected. Even where there are well-marked signs of disease, the examination should not be completed until the possibilities of the heart's state being aggravated from extrinsic causes can be excluded. This is particularly the case in febrile attacks, as the heart responds to the febrile state in a great variety of ways. Each microbe, which produces a rise of temperature, at the same time manufactures some toxin peculiar to itself, and this toxin often reacts on the heart. It is for this reason that in some individuals at one time the rate, with a slight rise of temperature, may be greatly increased, while in another febrile attack the temperature may be much higher and the rate of the heart beat much slower.

It should also be remembered that during a febrile attack the poison may induce varying degrees of dilatation of the heart, and systolic murmurs frequently arise during a simple febrile illness. The neglect of this may lead to the suspicion that the symptoms are due to the invasion of the heart itself by the disease, and it is not always possible to be certain whether the changes in the heart are due to a temporary poisoning or to the disease affecting the heart. The possibilities being recognized, the search for associated phenomena will help to settle the matter.

The Examination of the Patient

The Patient's Appearance.—In every instance, when a doctor sees a patient he should rapidly but searchingly scrutinize the patient's face, and note the manner in which he walks, or the position he assumes in bed. If he is in bed, the fact that he lies flat, or has to have his head or parts of his body raised, gives information as to how the heart maintains the circulation when he is at rest. On entering the doctor's presence the state of the patient's breathing should be noted, as well as his manner, whether calm and collected or betraying signs of nervousness and anxiety. The fact that a patient may consult the doctor under the impression that he has something wrong with his heart may throw him into a state of excitability that will react on the heart, and later on in the examination an increased rate of the heart may be referred to this cause and not taken as an evidence of cardiac trouble.

Pallor.—The color of the face gives much helpful information in many obscure cases. The healthy countenance needs no description, as it is one of those matters one knows and recognizes, and words fail to convey an adequate description of it. There is a tinge and a color which, even in the bedridden, at once puts out of count a number of conditions which might otherwise have to be considered. On the other hand, the color of the face often gives a clue to the nature of the condition, as in the anemias, and in cases where a subtle change occurs which may be, and often is, overlooked. As the anemia, which is the cause of the pallor, often induces cardiac disturbances, many people are supposed to have a heart affection because of these disturbances. While the different anemias may be described in terms corresponding with the results of a microscopic examination of the blood, a helpful appreciation of the condition can be acquired by the physician from the appearance of the patient's face. The pallor of the chlorotic and of the weakly, produced by unhealthy surroundings or prolonged ill-health, should be recognized and distinguished. When the physician sees these signs, he is at once given a cue that he will probably have to seek for some other cause of the patient's complaint than the heart. In the serious anemias, as pernicious anemia, the early stages of malignant disease, or the late stages of a microbic infection, the chief complaint may be breathlessness on exertion and palpitation, and the physician easily may be misled because he at the same time detects some abnormality in the heart. This is more likely to happen to the doctor who sees the patient frequently, as the progress of the disease is so insidious that he fails to note the gradual changes which are taking place in the color of the patient's face. Another doctor, seeing the patient for the first time, may have his attention arrested by the pallor. The pallor in these cases, as a rule, is different from that of chlorosis or the pallor of poor health, in that there is often a faint sallow tinge, and the face is a little drawn, a faint alteration in the expression difficult to describe. When any adult, in whom there is no reason to suspect either chlorosis or pallor from poor health or bad environment, shows such an alteration in color, the suspicion should always be aroused that there is some serious mischief present. I have repeatedly observed, particularly in elderly people, that a faint but definite change of this kind heralded the onset of a serious disease.

While the heart in these cases is only affected secondarily, a progressive pallor, it should be remembered, is an accompaniment of a steadily advancing and insidious form of malignant endocarditis. The pallor of empty capillaries, as after an attack of unconsciousness, due to standstill of the ventricle as in heart block (Adams-Stokes syndrome), is sometimes very intense. A persistent pallor, sometimes with a dirty color—"the earthy countenance"—is characteristic of certain cases of aortic regurgitation.

Cyanosis.—In many cases of advanced heart failure the blood is not sufficiently oxygenated, and the color of the cheeks and lips becomes altered, shading from a slight darkening of the red cheeks and lips to marked blueness. Although it is assumed that cyanosis is a sign of ineffective circulation through the lungs with diminished respiratory exchange, yet there is something else in the matter. Patients with manifestly diminished pulmonary circulation even with failing hearts, may show no signs of cyanosis, while others show marked cyanosis in whom there is no reason to assume that the pulmonary circulation is interfered with, and when there is no reason to suspect any communication between the right and left sides of the heart permitting an admixture of venous and arterial blood.

Although cyanosis is associated with a great variety of conditions which hinder the oxygenation of the blood from mechanical causes, and is sometimes due to poisoning from coal tar derivatives and certain toxic conditions of microbic origin, there are some in whom the cyanosis is undoubtedly cardiac in origin, and it is then typical of certain diseased states of the heart. One of the most striking is the florid cheeks, of a dark red, an appearance which is usually associated with a certain degree of wasting which occurs in a somewhat advanced state of auricular fibrillation, particularly when associated with mitral stenosis. The appearance of the face is almost diagnostic. It is often associated with a slightly jaundiced tinge, and in these cases the liver will be found enlarged. Some people have a "high color," a ruddy face but with a somewhat darker tinge, which many superficial observers would take to be indicative of robust health. I saw recently a young man of twenty-five who was passed as fit for the army because of his "full-blooded" looks. It was only when he called attention to a swelling on the backs of his hands and his legs that doubt arose. A careful examination revealed that he suffered from a fairly advanced stage of adhesive mediastinitis of tuberculous origin.

The cyanosis of congenital heart disease (morbus ceruleus) with clubbed fingers is well recognized, but how it is brought about I do not know, for it occurs in cases where there is no deficient septum between the right and left chambers of the heart. A considerable degree of cyanosis of the extremities is not usually cardiac in origin, and it may occur in healthy people, especially in lanky youths on a cold day. This is vasomotor in origin. Its presence in people with heart affections may mislead. I have seen an elderly man who had frequent attacks of auricular fibrillation, whose nose and lips became very blue when at rest. Exertion on going up and down one flight of stairs immediately dispersed the blueness.

The Interrogation of the Patient

Realizing the importance of the patients' sensations, great care should be taken to get a good knowledge of their experiences. The questions must be framed so that the patient recognizes what it is we ask, and it is, therefore, incumbent upon us to have a clear conception in our own minds of the kind of information we are seeking. Each question, therefore, must have a definite object, and must be put so clearly that the patient comprehends our meaning; we must also insist upon the answer being limited to the question, and we must not pass away from the subject until we have got as full an answer as the patient is capable of giving. This implies, on our part, a knowledge of the kind of information the patient is capable of yielding, and much training on our part is necessary for us to attain the skill of a competent examiner.

The first question bearing upon his condition should naturally be to ask of what he complains. The reply to this question should be limited to the sensations which immediately caused him to consult a doctor. Thus, if it is a heart trouble, he must clearly specify the sensations he himself experiences, as pain, breathlessness, or exhaustion. At first a note should be made of all the sensations of distress or discomfort of which he complains; then each sensation should be taken up by itself. Thus, if pain is complained of, the situation in which the pain first appeared should be found out, getting the patient to indicate this by placing his hand over the region; then the part to which it radiates, and the character of the pain, as to its intensity and duration, whether continuous or intermittent. The circumstances provoking the pain, as whether it is brought on by effort, mental excitement, or when the body is at rest, and its relation to food, should be ascertained. With these facts clearly appreciated, the first time the pain, even in its mildest form, was felt, and the occasion of its appearance should be elicited. Exhaustive inquiries of this sort should be directed to every other sensation, naturally modifying the question according to the character of the sensations. With the facts thus elicited, a fair perception of the nature of the complaint will be acquired and the inquiry then should be pursued as to illnesses and habits of life that may have induced the complaint. A brief inquiry into the functional efficiency of other organs, as sleep, the state of the digestion, menstrual functions and frequency of micturition, should be made.

As distinct from these inquiries, an inquiry must be made in all cases of heart trouble as to the efficiency of the circulatory system, by getting from the patient the amount of effort he is capable of undertaking without distress, as how far he can walk, whether his work entails bodily effort, and, if so, how it affects him; what games he plays and how he bears the effort. If there is a limitation of the response to effort, the time it was first perceived and the attendant circumstances should be noted. The nature of the sensations which limit the patients, as breathlessness, palpitation, pain, sense of exhaustion, should be elicited. From the character of these sensations we can gather whether the story of the patient is one of heart failure or of vasomotor disturbance.

In children some difficulty may be experienced in getting out the facts, but as a rule, it is easy to appreciate the heart's efficiency when they are old enough to talk and run about. Unfortunately, there is a mistaken idea in the minds of parents and physicians that a suspicion of heart trouble demands that a child should be kept at rest. No doubt in rare instances of acute or progressive disease, rest is necessary, and the need for it may be recognized by a physical examination. But a great number of children, who are supposed to have weak or impaired hearts and are able to run about, are often needlessly restricted, because of some physical sign, murmur, or irregularity. It should be understood that children with a heart, the efficiency of which is impaired, will not injure it by overexertion. Children are very sensitive to distress, provoked by cardiac inefficiency, and will themselves abstain without being told, and one can usually recognize the degree of inefficiency by getting the child to state if he likes running about with a hoop or running upstairs. When they say they like doing it and it gives rise to no distress, it may be considered, whatever the cause of the trouble, that it has not impaired the heart's strength. I cannot recall a single instance where I could reasonably attribute heart failure to a child's voluntary exertions.

The same reasoning applies to the games of boys and girls; when they exert themselves and find pleasure in doing so, it may be taken for granted that no harm results.

Affections of the Myocardium

In the description of heart failure it was shown that the efficiency of the circulation was dependent on the integrity of the heart muscle, and that diseases of the other parts of the heart produced heart failure by embarrassment of the heart muscle. It is not possible to give a description of any form of heart disease without understanding the condition of the heart muscle, and this can only be perceived by the evidences of heart inefficiency, although gross changes in the muscle may give rise to certain physical signs.

In the vast majority of cases the myocardial diseases cannot be clearly differentiated, and we are dependent for our recognition of them mainly on inferences drawn from the signs of heart failure. The pathological conditions revealed post-mortem usually show extensive changes in the myocardium, more often of a fibrotic kind, fatty degeneration of the muscle fibers being a comparatively rare condition. Degeneration of the coronary arteries, leading to fibrotic changes in the muscle, is frequent in the elderly. Sometimes we come across a case where death has ensued from heart failure with no naked eye or microscopic changes in the heart muscle which would explain the heart failure, and one can only infer that the functional efficiency of the fibers was impaired.

In the great majority of cases of chronic myocardial affection we are without any clue regarding the origin of the disease. We know that it occurs after rheumatic fever, and we infer that, during the acute stage, the myocardium may have been invaded by the organism that produced rheumatic fever. We can infer that a similar process occurs in other infections, and that after recovery from the acute stage a certain diseased state is left behind which ultimately leads to gross changes in the muscle wall. In the majority of cases we get no history of an infection to which we can trace the origin of the myocardial disease, but there is sufficient evidence to show that many seemingly slight and trivial infections can invade the heart and damage it. Thus during or after an acute affection, as rheumatic fever, typhoid fever, or influenza, the appearance of an irregular rhythm may show that the auriculo-ventricular bundle has been affected, which may be taken as evidence of the invasion of the heart muscle. Figures 1 and 2, for instance, were taken from a man after an attack of typhoid fever. I have on several occasions detected the same phenomena during mild and severe attacks of lumbago, or muscular rheumatism, and it is surmised that the fibrositis which affected the skeletal muscles also invaded the heart muscle.

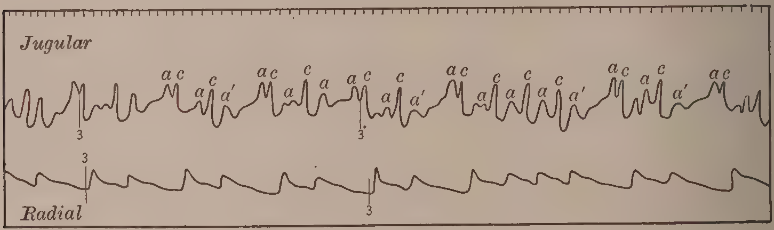

FIG. 1.—Simultaneous tracings from the vessels of the neck and radial pulse. The *c* waves are due to the carotid and are synchronous with the radial beats; the *a* and *a′* waves are from the jugular vein and are due to the systole of the right auricle. It will be observed that the *a′* waves are not followed by a carotid wave because the stimulus from the auricle does not always reach the ventricle on account of an impairment of the bundle connecting auricle and ventricle, thus giving rise to that irregularity in the action of the ventricle due to partial heart block. From a patient after typhoid fever.

The symptoms produced by a myocardium, the seat of disease, are identical with those produced when the muscle is weakened from toxic influences or poor nourishment, as in chlorosis and other anemias. This renders it impossible to say, in any given case, after a mild or serious febrile attack whether the heart has been damaged. The long persistence of signs of cardiac enfeeblement may lead to the suspicion of myocardial damage, but beyond that we cannot go. For these reasons the symptomatology in the early stages is not distinctive, and the milder symptoms are dealt with in connection with exhaustion and the soldier's heart.

After the subsidence of the symptoms provoked by the acute or subacute process, there may be a long period of seeming quiescence, when the individual may pursue a strenuous life with no evident impairment of his powers. In certain cases we can detect evidences of damage long before any noticeable failure of the heart appears, as in the persistence of a wide a-c interval in graphic records from the jugular pulse, evidence of a myocardial affection which has invaded the auriculo-ventricular bundle. The damage done to valves by an acute endocarditis is often progressive, as shown by the gradual alteration in the character of the murmurs in aortic regurgitation and mitral stenosis. In many of these cases the myocardium is affected at the same time, and here also the damage is not stationary but progressive. Probably in every case of myocardial disease there is, from the beginning, a slight impairment of the functional efficiency of the heart shown by a limitation in the response to effort. Unaware of this impairment, the individual attempts to lead the life of a healthy person, and the early symptoms of exhaustion are ignored. The increasing ease with which these symptoms are produced directs attention ultimately to the cardiac impairment. This recognition of the impairment may follow long after the original damage, the time depending naturally on the extent of the damage and the rapidity of its progress, and the amount of effort to which the individual has been subjected. In addition to the changes induced by acute affections, there is a series of cases where we cannot recognize the origin of the changes, but find them associated with other conditions, such as arterial degeneration, high blood pressure, kidney disease, sometimes with a history of alcohol or syphilis. These cases all pursue a similar course and show the same phenomena.

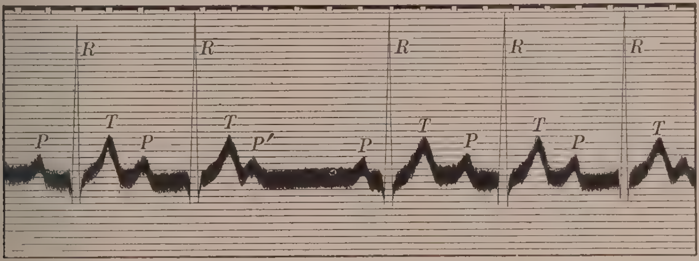

FIG. 2.—Electrocardiogram from the same patient as gave Figure 1. The waves *R* and *T* are due to the systole of the ventricles. The waves *P* are due to the systole of the auricles. The waves *P* are quite regular, but after the auricle waves *P′* there is no ventricular response, the stimulus from *P′* being blocked. Note the varying length of the *P-R* interval.

It is almost universally assumed that the heart failure in people with valvular murmurs resulting from infection, such as rheumatic fever, is due to the chronic valvular disease, and such cases are separated from those of heart failure with no murmurs, the latter being described as cases of chronic myocarditis. This distinction is scarcely justified, for the valve affection has often little to do with the heart failure.

Dilatation.—The evidence of dilatation of the heart is made out by marking out the increased size of the heart. I need not dwell upon how this is done, for the methods for percussing out the heart's dullness are described in sufficient fullness in every handbook of physical diagnosis. For practical purposes the transverse dullness at the level of the fourth or fifth interspaces gives on the whole the best estimate of the size of the heart. In exceptional cases the whole area of deep dullness may be mapped out with advantage, as when dullness is found extending to the left above the third rib. In such cases the possibility of pericardial effusion should be kept in mind.

It is very difficult to tell with certainty what share each chamber of the heart takes in the production of the increased size, on account of the displacement of the whole organ. The manner in which the heart is fixed above, by the aorta, the pulmonary artery and veins, and the superior vena cava, and below by the inferior vena cava, keeps fixed an axis on which the heart, to a certain extent, rotates in the enlargement of its various cavities. The tendency, when the right ventricle dilates, is for it to push the left ventricle to the left and behind, with the result that, in the great majority of cases of dilated right heart, we get evidence of an extension of the dullness to the left and only a slight increase to the right. When the right auricle becomes greatly distended, it may push itself to the front of the chest and compress the right ventricle to a remarkable degree. When there is extension of the dullness beyond the right border of the sternum, it may with certainty be put down to the right auricle, except in aneurysm or intrathoracic tumor.

When the right ventricle enlarges, it pushes the left ventricle further to the left and behind, so that in great dilatation of the right ventricle the apex is formed by the right ventricle. This can be recognized by the fact that the apex gives an outward thrust during systole when it is formed by the left ventricle and an indrawing during systole when it is due to the right ventricle. (By the term apex I mean that part of the heart that beats lowest and furthest to the left.) The epigastric pulsation, due to the dilatation of the right side of the heart, is also characterized by the indrawing during ventricular systole, and the outthrust during ventricular diastole.

When there is dilation of the left ventricle, the outthrust of the apex may be felt as far out as the mid-axillary line and in the seventh interspace.

Hypertrophy.—The cause of hypertrophy is invariably an increased opposition to the emptying of the chamber. The systematic exercise of the heart's action keeps the organ in a healthy condition. A cessation of systematic exercise tends to diminish the vigor of the organ and even to produce atrophy of its active tissues. An increase in the exercise tends to produce an increase in vigor and an increase in the active tissues, so that, within certain limits, we may speak of a physiological hypertrophy, meaning thereby a state comparable to the large muscles of a blacksmith's arm. In such cases the hypertrophy is moderate, and we no more get an abnormal hypertrophy of a healthy heart than we can get an abnormal expansion of the biceps as the result of exercise. This should be borne in mind, for there are certain terms often used, which are misleading, such as that of "athlete's heart." This term is intended to denote an abnormally hypertrophied organ. I doubt if there is such a thing and when my opportunities of observation are considered, I think it will be allowed that I would have seen it if it had really existed. I have, on the other hand, seen many cases that were called "athlete's heart," but a careful examination of them invariably revealed other conditions which had been erroneously attributed to the athletics.

Setting aside, then, the hypertrophy which is physiological, all other forms of hypertrophy invariably occur as a consequence of some morbid condition obstructing the work of a chamber of the heart. The most extreme forms of hypertrophy are found with aortic regurgitation and adherent pericardium. There is something peculiar in the hypertrophy of aortic regurgitation, for though the muscle wall undoubtedly increases greatly in thickness, I am not quite clear in my mind that the hypertrophy is an increase of healthy muscular tissue. In aortic regurgitation, if my doubts are justified, it is not therefore the obstruction to the output alone which causes the hypertrophy, for in aortic stenosis with no regurgitation, or with only a slight amount of regurgitation, we never see the same degree of hypertrophy. It is possible that the dynamic effect of the regurgitating blood may participate in the production of this hypertrophy, but so far as I have looked into the subject, I have not found any constant correspondence between the degree of hypertrophy and the extent of the aortic leak. Moreover, the muscle itself is often so manifestly inefficient that one cannot but suspect that the hypertrophy is not genuine, even though the microscope reveals nothing but apparently normal muscular fiber. On this point, indeed, I cannot see a clear issue.

The same unsatisfactory conclusion is reached in regard to the hypertrophy of adherent pericardium. An adherent pericardium does not necessarily cause hypertrophy, because one often finds an adherent pericardium on the post-mortem table when there is little or no increase in the size of the heart. On the other hand, if the pericardium is more or less fixed to the chest wall, in front to the ribs and behind to the spinal column, *e.g.* in adhesive mediastinitis, then the hypertrophy may be enormous. To a certain extent this hypertrophy can be attributed to the fact that the muscle of the ventricle has to drag in the ribs during systole; but I have found remarkable hypertrophy in cases of adherent pericardium of rheumatic origin when there was no attachment to the chest wall. In these cases, I fancy, there has been some myocardial condition favoring an increase in the muscle wall, but I have not been able to demonstrate it.

Very big left ventricles are often found in kidney disease and in cases with persistent high blood pressure. In these cases, no doubt, the arterial resistance is an agent in the production of the hypertrophy; yet it is not clear that it is the only agent. The conditions that affect the peripheral blood vessels affect also those of the heart itself, and thus, it may be, damage the muscle fibers. At all events, I have been struck by the post-mortem appearance of a number of my cases. These hearts have shown, towards the apex, large areas containing but few muscle fibers and a great amount of fibrous tissue. In these the muscle must have been seriously impaired years before the final breakdown.

In dealing with the significance of special hypertrophies, the matter must be considered along with the lesion producing them, as in valvular disease. A hypertrophy, due to any morbid cause, invariably indicates an inefficient heart. There has come into use a term "compensation" which is employed in a manner distinctly misleading. This term is often used in a vague and unscientific manner, and those who use it rarely explain what they mean. Thus, we will find an individual with a murmur described as having a "mitral leak with good compensation," although his heart is perfectly normal and physiological in every respect. A patient with orthopnea and dropsy from heart failure is spoken of as being in a state of "decompensation," and when the dropsy has disappeared and the patient can lie down, "compensation" is said "to be restored," though the patient's response to effort is permanently impaired.

SYMPTOMS OF CHRONIC MYOCARDIAL DISEASE

The symptoms of myocardial disease, beyond changes in the size and shape of the heart, are revealed by changes in the rate and rhythm of the heart beat, and there are always the signs of impaired efficiency, which are those of heart failure already described. In dealing in some detail with these latter phenomena it will be useful to separate them into two forms: (1) those belonging to the second group of symptoms in the classification of symptoms, *i.e.*, the functional group, where the symptoms are shown in remote organs because the heart fails to maintain an efficient circulation, and (2) those in which the symptoms arise from a stimulation of the central nervous system causing pain and allied phenomena. The first of these forms will be described here, the second in the chapters on cardiac pain.

Rate.—The rate of the heart in myocardial affections is extremely variable, and as the variation in rate depends on so many factors, it is not always easy to recognize the actual factor in any given case. In some febrile cases a persistent increase in the rate may be taken as indicating the presence of some agent which either weakens the myocardium by injury (as the fibrotic changes in rheumatic affections) or by poisoning (as alcohol and the toxins of infectious diseases). In great exhaustion increased rate is frequently present, and it may be that it is the increased rate which induces the exhaustion. With extreme degeneration of the heart muscle, the rate may not be altered.

Rhythm.—The different abnormal rhythms have a definite relation to diseases of the myocardium. Extrasystoles, auricular fibrillation, auricular flutter, irregularities, and abnormal rhythms due to injury of the conducting system and pulsus alternans, may all be the expression of an injured or impaired myocardium.

Size.—The evidence of hypertrophy of the left ventricle is mostly limited to the forcible thrust of the apex beat. But though this is often a marked sign, we not infrequently meet with a large forcible apex in very inefficient hearts, with very extensive degeneration of the left ventricle. The electrocardiogram may show a modified form when associated with hypertrophy of the different chambers and in its form indicate which chamber is preponderatingly hypertrophied. A forcible shock is found inside the left nipple in hypertrophy of the right ventricle. The pulsation of the liver due to the right auricle is suggestive of hypertrophy of that chamber, induced by tricuspid stenosis. Generally it is not possible to recognize the chamber or chambers which are most increased in size in dilatation or hypertrophy.

Breathlessness.—A deficiency of oxygen in the blood, or the accumulation of certain waste products in the blood, may stimulate the center of respiration to excessive activity. Hence a weak heart that fails at any time to send sufficient aërated blood to the respiratory center induces breathlessness. It may be that the heart cannot do this when the body is at rest, giving rise then to orthopnea.

Other factors may overstimulate the respiratory center rather than the failing heart, as certain blood states, the result of the anemias, and diseased kidneys, and mechanical conditions that interfere with the aëration of the blood in the lungs, and disease of the lungs themselves.

Breathlessness on Exertion.—The most frequent complaint in heart affections is, as we have seen, shortness of breath, which limits the patient's response to effort. A limitation of this kind is not, however, peculiar to cardiac sufferers. Many healthy people are short-winded, that is, they have so little reserve force that their store is speedily exhausted. What seems quite normal in them may, on the contrary, be due to some impairment in others. Thus, an individual who has been accustomed to take a considerable amount of exercise discovers suddenly a limitation of his powers. This may be very slight and may not at first attract much notice. Nevertheless the limitation may indicate cardiac inefficiency. We have already seen that the amount of reserve force available varies in healthy people. Bearing this fact in mind, we shall not experience great difficulty in discovering by means of a careful appreciation of the patient's sensations whether the limitation is normal or is due to impairment.

This breathlessness which arises as the result of effort, is a symptom common to all forms of heart exhaustion, slight and temporary as well as serious. But it occurs also in other conditions—*e.g.* lung affections and exhausting illnesses, so that no conclusion as to its real nature can be drawn until other phenomena have been investigated. A weighing of the resulting evidence will reveal which of the many provocative causes is at work in the case of the particular individual under consideration.

Breathlessness at Rest (*Orthopnea*).—When the breathing is labored while the patient is at rest, so that he is compelled to assume a sitting posture, the heart's impairment is so extreme that the "reserve force" is exhausted. But before deciding that the distressed breathing is cardiac in origin, we must exclude the various forms of respiratory disease which induce such extreme breathlessness—*e.g.* asthma, pleurisy, pneumonia, emphysema, and intrathoracic growth. When due to enfeeblement of the heart, the distressed breathing is generally the outcome of a long period of persistent overexertion. The real cause of the trouble is thus insufficient rest. In these cases the history may reveal the fact that the onset was gradual and extended over months or even years. Rest in bed will often of itself restore a certain amount of strength to the heart and cause the breathlessness to disappear gradually. When the breathlessness occurs rather suddenly, the likelihood is that it has been caused by the heart taking on an abnormal rhythm, for example, auricular fibrillation, in which the ventricle is stimulated to rapid and irregular action. Extreme breathlessness may set in within a few hours after the onset of auricular fibrillation though usually it does not appear for a few days or weeks.

Cheyne-Stokes Respiration.—There is a type of respiration in which the breathing ceases for a short period (ten to forty seconds), and then gradually begins again; from the period of cessation the breathing increases in intensity till a maximum is reached and then gradually subsides until it ceases. Sometimes these phases are very marked; at other times they are so slight that they cannot be detected unless the patient is watched during his sleep. This breathing, known as Cheyne-Stokes respiration, may occur when the patient is sitting quietly in his chair; usually, at first, it only occurs when he is asleep or dropping off to sleep. Sometimes the patient passes into sleep during the apneic period and may resume a conversation when the breathing becomes reestablished. Or he may continue to talk, but in a faint voice, during the apneic phase and return to his louder voice during the respiratory phase.

Cheyne-Stokes breathing is not usually discovered as a subjective sensation on account of the fact that many of those affected by it are quite unconscious of its presence. Its presence may be suspected when the patient describes suffocating sensations, which keep recurring when he drops off to sleep, or states that he awakes feeling suffocated. This sense of suffocation is usually due to recurrence of the apneic phase; sometimes it is so distressing that the patient will suddenly spring out of bed in an extremity of terror.

Cheyne-Stokes respiration has a varied clinical significance. Many elderly people with no particular disablement, beyond the considerable enfeeblement so common in advanced years, show it. In people with high blood pressure, advanced sclerosis of the heart and arteries, it is generally a sign of approaching dissolution. I have seen it in several cases of extreme heart failure, with auricular fibrillation and auricular flutter, and in these cases it had quite disappeared when the heart failure was relieved by digitalis.

Cardiac Asthma.—There is a form of dyspnea which comes on suddenly with great severity. It is so often associated with marked changes in the heart that it has received the name of "cardiac asthma," although this is not a very good term, as it tends to confusion with true asthma, which has no association with cardiac disturbance. It occurs most frequently in the night. The patient goes to bed and may fall asleep for a few hours; he is then awakened by a sensation of suffocation, which forces him to sit up. He breathes heavily and struggles to get into a position which will allow him to breathe with freedom. This dyspnea may last for half an hour or longer, and may then gradually subside, so that the patient is able to go off to sleep again. Usually, however, the patient remains propped up in bed, and if he sleeps, his sleep is troubled and disturbed, with a fear of the recurrence of the distress. The attacks resemble ordinary asthma and may be quickly relieved by a hypodermic injection of morphia.

This condition occurs most frequently in elderly people with degenerated heart muscle, high blood pressure, and changes in the arteries. These conditions may also, it should be noted, occur in middle life, and may be associated with albuminuria.

Cardiac asthma is a very grave sign, especially when it is associated with pulsus alternans and angina pectoris, and is usually a prelude of death, so that the duration of the individual's life can be reckoned by months; in milder cases, where the heart responds to treatment, life may be prolonged for a few years.

For some years I have been inquiring into the relation of this condition to Cheyne-Stokes respiration, and I find that the latter condition is present at times with cardiac asthma. I find again that in most cases the patient wakes in distress during the apneic stage, and the attack of severe breathlessness, which then develops, is identical with what is called cardiac asthma. I am in consequence disposed to look upon Cheyne-Stokes respiration as the origin of the attacks of cardiac asthma in all cases.

Dropsy.—Edema of the subcutaneous tissues is a common feature in heart failure with dilatation of the heart. It begins first in the most dependent parts. In people not confined to bed it is found first about and above the ankles; in people lying in bed, across the sacrum. It may linger in the legs for years in some folks—worse towards night, better in the morning. In extreme cases, it invades the thighs and abdominal wall. The loose cellular tissue of the scrotum, penis, and vulva becomes infiltrated, and the swelling may attain an enormous size. Before marked effusion takes place in the abdominal cavity, the bowels often become greatly distended with flatus. The effusion may finally invade the pleural cavities, producing hydrothorax. The distended abdomen and the hydrothorax add to the embarrassment of the breathing. If the patient leans more to one side than to the other, in extreme cases, the arm and cheek of that side may become greatly swollen.

Associated with dropsy, there is usually a diminished urinary secretion, and disappearance of the dropsy usually coincides with an increased flow of urine.

The significance of edema is extremely varied. Many elderly people, especially if they are stout, may for years have their legs more or less swollen, even if their hearts present no particular abnormality beyond a slight dilatation, though it is more common amongst those with auricular fibrillation. It may be present in attacks of heart failure to an extreme degree, with ascites and hydrothorax, and notwithstanding the patient may make a good and lasting recovery. These are found more particularly in cases of rheumatic affection of the heart of some duration, particularly with auricular fibrillation. In this condition, if the heart reverts to its normal rhythm, the disappearance of the dropsy is more speedy than its onset. If the heart reacts to digitalis, the disappearance of the dropsy accompanies the other beneficial effects of the drug. When all attempts to restore the heart fail the dropsy increases, embarrasses the heart and the respiration by effusion into the serous cavities, and adds much to the suffering of the patient, who drifts to a fatal issue.

In extreme heart failure, we may find a localized edema of one arm. This results from the patient lying on that side. If it is not on the side on which the patient lies, then it is due to a thrombosis of the superior vena cava. So extensive may this be that the clot may extend up into the jugular vein, and along the subclavian into the brachial. In such cases, there will be no jugular pulsation on that side, while it may be very marked on the opposite side.

Dropsy and Dilatation of the Heart.—One of the reasons inducing me to include dropsy as a symptom of dilatation of the heart, is that I am doubtful if it is possible for dropsy to occur from heart failure without dilatation. I see, not infrequently, cases of dropsy and enlargement of the liver diagnosed and treated for heart failure because there is a valvular murmur. In these cases there has been no increase in the size of the heart, and I have therefore assumed that the dropsy was not cardiac in orgin. The subsequent progress of the cases revealed that there were other causes for the dropsy (as cirrhosis of the liver or myxedema).

Enlargement of the Liver.—Another result of the failure of the circulation secondary to dilatation of the heart is swelling of the liver from passive congestion. It may not appear in the earlier stages in the first instance, but when a patient has once recovered from an attack of heart failure with enlargement of the liver, every subsequent attack induces this symptom, sometimes before any sign of dropsy sets in.

There may be associated with the enlargement a certain amount of jaundice, and the combination of enlarged liver and jaundice with the wasting that sometimes accompanies long-continued heart failure may raise the suspicion of malignant disease of the liver. The dilatation or irregular action of the heart should direct attention to the real nature of the trouble.

There may be a considerable degree of pain and cutaneous hyperalgesia associated with the enlargement of the liver. The muscles of the abdominal wall may be contracted and hyperalgesic so that they embarrass the respiration.

Edema of the Lungs.—A symptom of great value is found in the careful auscultation of the bases of the lungs in cases threatened with some forms of heart failure, as was pointed out in dealing with heart failure in the bedridden.

Urinary Symptoms.—I doubt if ever we get the characteristic urinary symptoms of heart failure in the absence of dilatation of the heart. These symptoms are a scanty excretion, increased specific gravity, and frequently the presence of albumin. A diminished supply of blood to the kidneys may cause a large quantity of albumin to appear in the scanty urine, as can be observed in heart block, when the heart's rate becomes very infrequent. The diminution of the quantity of urine excreted usually goes hand in hand with the dropsy. The cause in the main is a fall in arterial pressure and a rise in the venous, with consequent venous stasis in the kidneys. Other conditions may cooperate, such as the chemical constitution of the fluid in the tissues and changes in the secreting cells of the kidney. It is often a difficult point to determine whether the albuminuria has been preexistent, or whether it is induced by the venous stasis and subsequent inflammatory changes in the kidneys. The history of the patient will help and the presence of arteriosclerosis and retinitis points to a preexistent Bright's disease. It may be necessary to suspend judgment until a recovery of the heart restores the circulation, as with the increase in flow of urine the albumin may entirely disappear.

It is often useful to direct the patient's attention to the urinary excretion, as its diminution may give the first warning of an impending breakdown, and the increase in the flow is often the first sign of recovery of heart power.

Heart Pain (Angina Pectoris)

When a healthy person runs until his heart becomes exhausted, he is compelled to desist by breathlessness, or a sensation of oppression across the chest, sometimes accompanied by pain. Pain can arise from the action of any muscle in health, when that muscle is made to contract to an excessive degree, or is forced to continue working after fatigue is produced. When pain arises in a muscle affected by disease, the symptom is produced in the same manner as in health, only the exhaustion, of which it is the evidence, is more readily induced and the pain therefore appears with greater facility.

If it is appreciated that the pain in heart affections is but a symptom which is capable of being evoked in all hearts, the only difference between its appearance in health and disease being the greater ease by which it is produced in the diseased heart, a good idea is obtained of the seemingly intricate and complicated phenomena which we call angina pectoris, and which can therefore be looked upon as an expression of exhaustion of the heart muscle. With this conception in mind, we are put on a track which leads to a clear view of the patient's condition. If in health, exhaustion from overexertion induces pain, in impaired health with a weakened heart muscle, if pain is easily induced, we are led to inquire into the cause of the premature exhaustion. In people who suffer from any debilitating state, the heart likewise suffers, and consequently in them we may get heart pain readily induced. Although the heart pain may be a dominant symptom, if we recognize that the heart condition from which it arises is provoked from some other source, we are at once directed to search for causes that may tend to debility. When extraneous causes of cardiac debility can be excluded, consideration is given to the state of the heart, as naturally a disease of the heart which impairs its functional efficiency will be apt to produce pain. Here, however, we are met with a difficulty. If a number of patients be examined who present different symptoms and their hearts are examined after death, diseases seemingly identical may be found present in the heart. Thus the coronary arteries may be found diseased with degenerative changes in the heart's muscle. During life pain was the chief symptom in a few, while others suffered no pain. In cases of aortic disease pain is sometimes a clamant symptom, while in others pain never occurs. In the hypertrophied heart associated with kidney disease pain is occasionally a very distressing symptom, while in others no pain is felt.

That these differences should bewilder and confuse and lead to a great many theories as to the cause of pain in heart disease is but natural, and we have many people who strenuously support this or that view, and each supplies many facts which he claims support his view. Some indeed would refer the pain to the state of the nervous system, some patients having a nervous system more susceptible to pain than others, and they have no difficulty in getting facts to support such a view.

At this stage of knowledge it would be unprofitable to enter into a discussion of the subject. We are far from having a clear conception of all the facts that would enable us to explain the mystery of cardiac pain. Too little is known of visceral pain, even in its simplest forms, to enable us to understand all the factors concerned in its production. But the fact is there before us, of pain of a very distressing character which the doctor must do something to relieve, while he may be unable to understand exactly how it is brought about. While disclaiming, therefore, any intention of giving an explanation of how pain is produced in heart affections, I propose to discuss certain aspects of the matter which have a bearing upon practice, inasmuch as this gives a view which enables one to carry out measures of relief, and affords grounds for rendering real benefit to the patients.

The view that pain is an expression of exhaustion of the heart muscle gives the best idea of the nature and extent of the heart's impairment in grave affections of the heart as in milder affections. The association of angina pectoris with disease of the coronary arteries is so well recognized that some take it as an evidence of coronary disease, and the pain is supposed, in some way, actually to be produced by the artery itself. If, on the other hand, we look upon the disease of the artery as preventing an adequate supply of blood to the heart muscle, so that exhaustion of the heart is brought about very speedily when effort is made, a better idea is formed of the nature of the complaint. Experiments have shown that when the heart is made to increase its work the coronary arteries dilate and supply the heart muscle with a greatly increased supply of blood. If disease of the coronary arteries prevents this increased supply, we can understand that the exhaustion of the heart muscle becomes readily produced. In certain people the degree of effort the heart is forced to make corresponds to the frequency and severity of attacks of pain.

With this conception of the cause of cardiac pain, and I repeat I employ it chiefly because of its practical bearing, we are placed at once in a position for treating patients in a rational manner. When pain or other evidences of sensory disturbances are present, the conception of an exhausted heart at once arises. This puts us on a track to find out the causes of exhaustion; whether the circumstances and environment of the patient's life give occasion for exhaustion, as overwork, worry, sleeplessness, poor food; or whether any condition is present which lowers the vitality, as toxic influences from bacterial infections, intestinal stasis, diseases of other organs; or whether there is an obscure disease of the heart as shown by certain physical signs as the presence of valve defects which embarrass the heart in its work, kidney disease with arterial resistance, or other changes that hamper the heart and tend towards exhaustion. Lastly, there are the changes frequently found in the coronary arteries, associated with advancing years, in people in whom there are no perceptible signs of heart disease, either in the size or rhythm of the heart or the sounds of the heart. Confirmatory evidences of a diminished capillary field are often found in the thin and atrophied skin, and the thickened radial artery, from which it can be inferred that similar changes have taken place in the arteries of the heart, with a consequent diminished supply of blood to the muscle.

Features of Cardiac Pain

The points to be noted in the pain due to heart trouble are the site in which it is felt first, and the regions into which it spreads; associated phenomena, as hyperalgesia of the skin and muscles; the circumstances under which it occurs, and the nature of any provoking agent (effort, exposure to cold, excitement, food).

The region in which cardiac pain is felt is a very characteristic one, being usually in the left side of the chest. It frequently spreads to the inner side of the upper arm and forearm—the region shaded in Figs. 3 and 4. This region corresponds to the peripheral distribution of the lower cervical nerves (6th and 7th in the arm) and the upper three or four dorsal nerves (in the upper arm and the chest). When pain occurs in any part of these regions, the question of its being of cardiac origin should arise. In some the pain may radiate to similar regions in the right side and in rare instances the pain is wholly right sided. I have not been able to make out any peculiarity in the heart that should account for the distribution of the pain on the right side. In a few cases the pain may also be felt along the lower jaw and behind the ears.

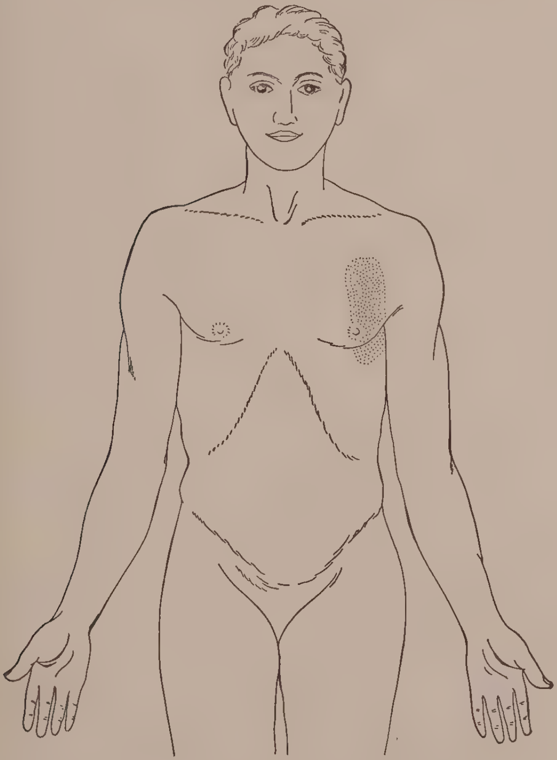

FIG. 3.—The shaded area shows the situation of the pain and distribution of cutaneous hyperalgesia after the first attack of angina pectoris.

The starting of the pain is usually across the chest, about the level of the third ribs, or as low as the fifth ribs (Fig. 3). It may, however, arise in any part of the left side of the chest, or in the upper or lower left arm. When it starts in the chest it may remain fixed there, but usually it spreads across the chest and into the left arm. If it arises in the arm, it spreads to the chest. After it radiates, it remains fixed for a shorter or longer period with greater severity in one place, either in the chest or in the arm.

The duration of the pain may be for a few seconds, yielding at once on the cessation of some provoking cause, or it may remain for a few minutes or last with slight variation of intensity for many hours. A dull aching, not of much severity, may be present off and on for days. An increased sensitiveness to pain (hyperalgesia) in the areas of skin over and around the left breast is often present in women. The patient is sometimes conscious of this tenderness, and any pressure hurts, as when the clothing is rather tight. It is elicited by lightly pinching the skin between the finger and thumb or by direct pressure with the finger. Other structures than the skin are sometimes very tender, as the pectoralis major muscle where it

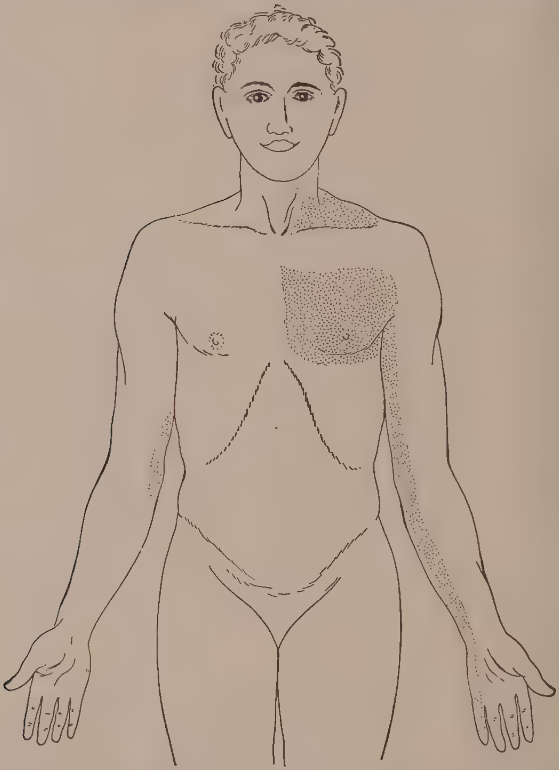

Fig. 4.—From the same patient as Fig. 3 after repeated attacks of angina pectoris. The pain and cutaneous hyperalgesia extended to the regions shaded here. Note the areas in the neck and inner side of the left elbow.

forms the anterior wall of the axilla. Here, if one grasps the muscle, the pain is felt acutely. The left sternomastoid muscle, and the upper border of the trapezius muscle are also frequently found to be tender on pressure. Tender points may be found in the chest wall where branches of nerves are pressed upon, and the lower cervical and upper dorsal vertebrae are also sometimes tender on pressure. The hyperalgesia is not a frequent sign in men with severe angina pectoris, but is common in the cases of debility due to some general toxic cause, especially among women. Its extent or intensity is not related to the gravity of the heart trouble.

Associated with the attacks of pain are other reflexes; the most frequent and the most instructive is the sense of constriction of the chest. This may be limited to a slight uneasiness across the chest and it may never get beyond that. Frequently this slight uneasiness gradually increases until the chest is held as if in a vise, and the sensation, because of its severity, carries with it a sense of fear. It is independent of the pain, and may be present without the characteristic pain, though both sensations are often combined. I am disposed to look upon it as due to the violent contraction of the intercostal muscles, resembling that contraction of the abdominal muscles so well known in diseases of the abdominal viscera. A study of its peculiarities shows that it is identical with the spasm of muscles in pleurodynia. It is of importance to recognize this sensation of constriction, as it is often the first sign of the oncoming heart exhaustion. In a large proportion of cases liable to severe attacks of pain as a result of effort, the first sign that the heart is becoming exhausted is a slight sense of constriction. When this occurs while walking, if the patient slows his gait or stops, the sensation at once disappears. If, on the other hand, he ignores the sensation and tries to "walk it off," it increases in severity and the pain appears and the consequent suffering becomes so great that the patient is compelled to stop. This severe stage may not be reached in the early days of the appearance of the signs, but if neglected, the exhaustion of the heart gradually increases until its neglect is followed by the greatest distress. I will point out later how a recognition of this sign helps in treatment and in giving a guide to the patient in regard to the amount of physical effort he may undertake. A curious matter in relation to this is that many men who have a tendency to angina pectoris, recognize that this sensation of constriction is the same sensation which used to compel them to stop when in their youth they ran to the limits of their endurance, so that its production in later years is but an indication of a greater limitation of the field of response to effort.

Accompanying this sensation of constriction, there is frequently a sense of suffocation, a feeling as if the throat was being compressed, and referred to the neck immediately above the sternum. This sensation is, I think, produced in the same way as that of constriction, though I cannot make out the muscles that are affected.

Other reflexes produced at the same time as the pain are occasionally present, as a flow of saliva and increased urine excretion. There is also often present that sense of collapse allied to shock, if it be not the same thing as shock, which results from a violent stimulation reaching the central nervous system by way of the cardiac sympathetic nerves.

Pain and the other reflex phenomena appear in so many kinds of heart affections, from those suffering from gross disease to others with healthy hearts temporarily exhausted, and we are so ignorant of many factors necessary to a full understanding of the condition causing pain, that it is impossible to present the matter in a way that embraces the whole subject. I think, however, the matter may be presented in such a way as will be found of great use in practice, in separating, for instance, the grave from those of little significance, and in obtaining indications for treatment.

Recognizing that pain may arise from hearts affected by disease, and in hearts in which there is no structural lesion but where the muscle is weakened by influences which produce exhaustion, as overwork, poisoning, or impaired nutrition, we obtain a division which not only serves for a discussion of the subject, but when the differences are appreciated, places us in a position to diagnose correctly the great bulk of cases. These two groups will be discussed under the heading of (1) angina pectoris from diseased hearts, and (2) angina pectoris due to toxic and debilitating causes (see Chap. VII).

Angina Pectoris in Diseased Hearts

The tragic circumstances associated with certain forms of angina pectoris have so impressed the medical profession as well as the general public that any suggestion of the presence of such a condition conveys with it a sense of grave danger. That there are cases in which the occurrence of pain indicates a serious state is undoubted, but if it is understood that the pain is but an expression of exhausted muscle, and that, in the vast majority of sufferers, the exhaustion is not due to any serious form of disease, a truer appreciation of the condition will be obtained. Nor must the estimation of the gravity of any given case be based upon the degree of suffering, for a severe attack of pain is not necessarily dangerous, nor are the mildest attacks free from a dangerous significance. The importance of the symptoms must be estimated by an examination of the conditions that have provoked the exhaustion of the heart muscle. To recognize that, I have analyzed the records of many hundreds of cases, and though the analysis is not complete, yet it has afforded a very safe basis on which a fairly satisfactory prognosis can be given and a sensible line of treatment suggested.

The division of the cases into the following groups affords a means of presenting the essential features of the great majority of cases.

1. People in advanced life, about fifty-five and over, in whom the changes in the arteries are leading to a deficient supply of blood to all the organs, and in whom the arterial changes are more advanced in the heart.
2. People in whom the arterial changes are proceeding in the heart with greater rapidity and the disease is not capable of being checked and a fatal issue speedily follows.
3. People with damaged valves, especially with aortic regurgitation.
4. People whose hearts are embarrassed by having to labor against arterial obstruction, as in chronic disease of the kidney with high blood pressure and with damaged arteries.
5. A small indefinite group comprising rare conditions impossible to classify.

Group 1.—Elderly people show certain signs which we recognize as being but manifestations of advancing years. These changes present different features in many people. In many the most evident signs are alterations in some portion of the circulatory system. The skin, for instance, becomes thin, and the capillary supply to the skin is greatly diminished. The arterial walls become thickened and a cut made through the skin and subcutaneous tissues is not accompanied by that abundant oozing which we see in the young. Rather it is more venous in character with spurting from a few, small, thick-walled arteries. These changes, which are so evident in the external body wall, take place in deeper organs and naturally impair their functional efficiency. So far as the heart is concerned, this is shown by an exhaustion of the reserve force, shown by a restriction of the field of response to effort. In some this exhaustion of the reserve force is manifested by breathlessness, in others by pain.

The pain in these cases does not come on all at once. A man approaches his sixtieth year accustomed to a good deal of bodily exertion which in the past he has done easily and in comfort. As time goes on there arises a feeling that the effort is not performed so easily as it used to be done; he is more tired at nights, or on going up hills there is a slight constriction across the chest which he ignores or tries to throw off by a spurt; often he attributes it to indigestion. For months this may disappear, then it may recur, and at last, it may be after a long period of rather exhausting work or after some rather severe form of effort, he is seized with a pain of great severity. The attack may be of short duration, or it may linger on for hours, waxing and waning in severity. If the patient and the doctor do not recognize the nature of the trouble and the patient resumes his ordinary life and exposes himself to fatigue, these attacks will tend to recur and become easier of production until a period of rest is taken. If the patient be seen by a doctor who recognizes the nature of the trouble, simple modifications of the mode of life will enable him to resume his occupation, and by living at a lower level he may lead a useful life for many years with no recurrence of the attacks. On the other hand, the patient may be frightened by being told he has "angina pectoris," or the doctor may not use the expression for fear of frightening, but hints vaguely at some obscure heart condition that compels restriction and a course of treatment, and thereby reduces the patient to a miserable invalidism.

There are certain features by which this group may be recognized and distinguished from the next group. In both groups there is often no physical sign which throws any light upon the case, and we have to depend entirely for information on the patient's description of his experiences. It may be some time after the first attack, or series of attacks, before we can say definitely to which group he belongs. This decision is arrived at by allowing the patient to get up and about as soon as he has recovered from the exhaustion that usually follows an attack. He is permitted to walk so long as he feels no discomfort, but as soon as he feels the slightest sign of discomfort in the chest, as a slight constriction or sense of suffocation, he is at once to stop. It may be a few weeks or months before the tendency to the attacks disappears. After that the recovery is generally so good that he can resume his old occupation. By and by the patient will discover that the tendency is still present, as some indiscretion in exertion will remind him of the trouble by the appearance of slight aching across the chest. Moreover, there are certain circumstances which favor the return of the pain, such as walking after a meal, or on going out on a cold day, or walking against a cold wind. In addition there are, in some, recurrent periods during which the attacks become easily provoked, it may be when associated with some digestive disturbance. In fact, the close association of the attacks with flatulence often misleads doctor and patient as to the origin of the suffering and treatment directed to the stomach condition meeting with success, in the sense that there is a temporary relief, too often confirms the notion that the suffering is mainly digestive. This also happens with the use of tobacco. In some people, liable to attacks of pain with structural changes in the heart wall, the use of tobacco tends to provoke the pain, and the assumption is that the tobacco causes the condition, so we have the condition described as a "tobacco angina." In all cases of this kind that I have watched sufficiently long, the pain after a time recurred if the tobacco was stopped, usually in response to exertion, so that there is no doubt that in such cases there are actual changes in the muscle. The position seems to be that in those predisposed to attacks of angina, tobacco is one of the factors that tend to provoke attacks.

In some cases belonging to this group the attacks of pain are at times so easily provoked that the suspicion may arise that the disease is so far advanced that these belong to the next group. The test I find most reliable is to recognize how much effort the heart can stand under the most favorable circumstances. If the patient can walk several miles in comfort at any time, then that is an evidence that there is still a good deal of healthy functioning heart muscle. As years go on these people pass on to old age and suffer and die from the infirmities which accompany old age, sometimes from the gradual exhaustion of the heart, sometimes from a cerebral hemorrhage, or more commonly from incidental illnesses as bronchitis or pneumonia.

Group 2.—The degeneration of the arteries of the heart may proceed more rapidly, and the heart's strength becomes reduced with greater rapidity than in the last group, so that death follows much more speedily after the first appearance of the pain. In the patients of this group the history of the pain shows that it becomes easier of production and tends to increase in severity from the date of its first appearance, until it culminates in a series of attacks which call attention to the gravity of the condition. In a few, a period of rest may result in a long spell of comparative freedom, but the attacks tend to recur with ever-increasing ease, and the heart's strength becomes so exhausted that it is incompatible with life, and the patient either dies suddenly during an attack, or a series of attacks supervene and he gradually sinks.

As a rule the signs appear earlier in life in this group than in the last, in the late forties or early fifties. The youngest age among my cases at which this pain appeared was a man of forty-three, and he died at forty-six. I am always anxious when men begin to complain of this pain before fifty years of age—not women, for reasons I shall deal with later. It is my custom in seeing this type of patient to insist on four or five weeks' rest, not confined to bed, but mostly on the couch, and be guided by the extent of improvement. In a great many there are no physical signs, and I have had several patients die within a few months of having their lives insured for large sums. A careful inquiry elicited from the patients that they had suffered from "indigestion" which on questioning revealed the pain to be situated in the chest and arm (see Figs. 3 and 4) and to be frequently provoked by effort.

The post-mortem examination in all the cases I have had the opportunity of making, revealed an advanced condition of disease in the arteries of the heart with fibrotic change in the heart muscle. One suspects syphilis as an agent, but the majority of the patients deny ever having it, and I failed to get any other evidences, though I did not always use the Wassermann reaction.

Group 3.—In this group the pain is associated with disease of the aortic valves. There is some peculiar relation of disease of and around the aortic valves to the nervous system and its reaction on the heart which has a very important bearing upon the health of the patient. We recognize the dilatation of the peripheral vessels as shown by the beating of the carotids and other superficial vessels and by the high systolic pressure and the low diastolic that gives rise to the Corrigan or water-hammer pulse, which is attributed to the regurgitation of blood back into the left ventricle during diastole. Regurgitation is a factor in producing this characteristic pulse, but it is not the whole cause, for the dilatation of the arteries and the arterioles is brought about by the action of the vasomotor nerves. There is, in some cases, an extraordinary sensitiveness of the vasomotor mechanism, such as I have not found in any other condition, shown by great variation in the blood pressure. Thus a patient may be lying in bed and feeling quite comfortable, but if disturbed or excited the blood pressure may speedily increase by 30 to 40 mm. of mercury. The curious fact that, by the ordinary methods of blood pressure measurement in use, the blood pressure in the vessels of the leg is much higher than that in the brachial artery, suggests some factor difficult to understand, provided that the methods employed are reliable.

Another matter in this relation to the nervous system is the association of pain with aortic disease. Though exhaustion of the heart produces pain associated with mitral valve disease, the pain is not so frequent nor so severe as in aortic disease. Here the attacks are often of the most painful kind, and provoked in a peculiar way. In some the pain accompanies the rise of blood pressure just mentioned, and the patient may roll about in agony till it subsides. Temporary relief may be obtained during the transient lowering of the blood pressure by one of the nitrites, to return again as soon as the effect of the nitrite passes off. In others the pain is provoked during periods of exhaustion, such as occur with persistent sleeplessness. Others occur at times from no apparent cause, *e.g.* in men able to do heavy bodily work without distress, as in a joiner I had under my care, who usually suffered greatly on first getting out of bed, but could follow his work all day without pain.

These experiences relate to cases of long standing aortic regurgitation arising from rheumatic fever or syphilis, or from those senile changes which damage the aortic valves. Though in some cases the attacks of pain are indicative of approaching dissolution, many live for many years after the appearance of the pain.

In more acute affections of the aorta, as in syphilitic aortitis, pain of a very severe character may be the first indication that there is anything wrong, and, before there is much valve destruction, death may supervene. Pain arising in a young man with no demonstrable sign in the heart, with a history of syphilis, should always arouse the suspicion of an aortitis. When accompanied by a regurgitant murmur, the diagnosis is practically assured, and a serious condition recognized as calling urgently for the use of anti-syphilitic remedies.

The pain in aortic disease is so characteristic that eminent clinicians like Sir Clifford Allbutt consider that the pain in all cases of true angina pectoris is aortic in origin.

Group 4.—In this group, where there is high blood pressure usually associated with or due to Bright's disease, attacks of angina pectoris are apt to appear during the later years of life. The condition is always well advanced, and the heart's exhaustion extreme. There is always considerable enlargement of the left ventricle and the arteries are usually thick and leathery and the arterial pressure ranges from 200 to 250 mm. of mercury and over.

I group these cases together because they have a correspondence and a resemblance in the stage in which angina pectoris appears, in the sense that attacks of angina pectoris occur when the heart is so damaged that there is no prospect of recovery, and when there is associated a series of phenomena which appear along with angina pectoris, all indicating extreme exhaustion of the heart muscle, such as Cheyne-Stokes respiration, pulsus alternans, orthopnea, and dropsy. In some, one of these symptoms may only be present and dominate the picture, or several may appear together. The previous history is very variable. There may be a history of albumin in the urine for thirty years before any one of these symptoms appears. On the other hand, a patient may consult a doctor because of his being pulled up by pain or breathlessness on making some effort he used to do in comfort, and the doctor finds a high blood pressure or slightly enlarged heart and no albumin in the urine. In spite of all care and attention, the patient develops albuminuria and Cheyne-Stokes respiration appears and he drifts and dies within a couple of years after the appearance of his first symptoms. On the other hand, occasionally we come across a man about seventy with a blood pressure of 240, feeling fairly well, who carries on in fair comfort for seven or eight years with little suffering beyond a tightness or slight pain across the chest on exertion till the later months of his life.

The anginal attacks in these cases are therefore but one of the evidences of an advancing failure of the heart which we can do little to check.

Group 5.—In certain diseases of the heart, attacks of angina may appear, as in adhesive mediastinitis or other conditions whose nature may not be understood but which show signs of gross disease. There are also met with, in the course of years in practice, attacks of illness of an unexpected kind which are so unusual that the doctor is often baffled to account for them. Amongst my notes there are a number of cases in whom attacks of pain, undoubtedly cardiac in origin, occurred and presented features so unusual that I am unable to explain them or to include them in any of the foregoing groups. A man of a gouty habit had several seizures of severe pain in the chest and arms accompanied by collapse, followed for weeks by a sense of prostration at the ages of forty-seven and forty-nine. He quite recovered and led an energetic life, and is today seventy-three years of age and in good health.

I was summoned in the middle of the night to see a man aged forty-one suffering from severe pain across the chest with a sense of impending dissolution which was only relieved by a hypodermic injection of morphia. He had not felt very well for a day or two before, suffering from a tightness across the chest on walking, but had thought little of it. I could detect nothing amiss except a to and fro pericardial murmur which disappeared in a couple of days, and the man made a good recovery and ailed nothing for many years after. He died twenty-four years later, but I do not know the cause of death.

A man fifty-five years of age, in good health, had been indulging in a series of dinner parties, and after a rather Gargantuan feast was seized in the night by a pain of great severity over the chest and in both arms. The pain was of a dull aching character and waxed and waned. The patient could not sit still but kept shifting about to get an easy posture. There was no sense of collapse. The pain only yielded to a sedative (veronal). Next day the patient was quite well and suffered no more from heart trouble save that in later years he noticed occasionally a slight aching across the chest on going up hill, but otherwise he is well and vigorous at the age of sixty-six.

A doctor aged fifty wrote me that he had a few attacks of great pain occurring when at rest. The pain was typical of angina, he said, being situated across the chest and down the arms. At other times he felt quite well and could play a round of golf with no distress. Nothing could be detected amiss on examination. I replied that there might be some infection present, and after six weeks he wrote that he had another attack and, for a few days, there was a pericardial to and fro murmur which completely disappeared. I saw him after this and he seemed quite well and was working hard. A few months later he wrote to make an appointment to see me, but telegraphed on the day of the appointment that he was too ill and wrote later saying that he had coughed up a large quantity of blood-stained frothy phlegm. Two weeks later he died in an attack of suffocation—edema of the lungs.

Angina Pectoris in Its Relation to Sex

The vast majority of patients who suffer from angina pectoris due to actual disease as distinct from toxic or other debilitating causes are men.

There are a goodly number of women met with whom one would put in Group 1, but exceedingly few in Group 2. In fact I only have notes of a few of this kind and they are not quite distinctive. In aortic disease women are perhaps more liable to attacks of pain than men. In the fourth group, though high blood pressure is fairly common in women, I have not seen many with the extreme form of heart failure. Attacks of pain have not the same grave significance, as the greater sensitiveness of the nervous system of women permits the appearance of sensory phenomena at a less advanced stage, so that we get with high blood pressure cases in women who have slight aching across the chest with hyperalgesia long before there is any serious degree of heart failure.

Conditions Favoring Attacks of Pain

While the immediate cause of the pain is dependent upon a variety of affections of the heart, the circumstances that induce an attack are also variable. To understand the matter it is necessary to recognize the extent to which the nervous system is involved. That angina pectoris is the outcome of a stimulation of the central nervous system is so manifest that it needs no comment, but it is necessary to recognize certain features which have an important bearing on the subject.

Any condition which produces exhaustion of the heart also produces exhaustion of the nervous system, and as the heart shows its peculiar evidences, so the nervous system exhibits its own evidences of exhaustion. One of these is an increased sensitiveness to stimulation. This is typically seen in men, and particularly in women, who have suffered from conditions that have produced debility, as overwork, want of sleep or illness of any kind. These people, when they continue to make physical effort beyond a certain limit, produce exhaustion of the heart, and this is often accompanied by variable degrees of pain. Frequently there is a persistent hyperalgesia of the skin, a sure indication that some part of the central nervous system is in a constant state of increased excitability.

This excitability can be inferred from other evidences. A patient may have attacks of pain, at first at rare intervals, but by persistence in the cause that produces them, as overexertion, they become more frequent and easier to be produced. In some, sleeplessness produces such a degree of irritability that the attacks are produced by slight causes, as exertion or excitement. It might be said that this is due to an increase of the stimulus from the heart and implies a greater degree of exhaustion, and in many instances this would seem to be true, for towards the end of life the pain may come on with very light provocation, or no apparent provocation. On the other hand, one can in certain rare instances provoke the pain from a stimulation independent of the heart. Thus, in a boy with a greatly enlarged heart from adhesive mediastinitis, the slightest stimulation of the skin under the left nipple would produce an attack. In another case, a few days before death, a patient could not raise his left arm without producing an attack, while he could raise his right freely.

The reason I dwell upon this point is that its recognition gives an indication for treatment, inasmuch as treatment directed to the nervous system rather than the heart sometimes affords relief.

Prognosis of Angina Pectoris

The view that angina pectoris is but the expression of an exhausted muscle and that the exhaustion may arise from any cause that overtaxes the heart, gives a means for forming a fair prognosis in most cases. I have already pointed out that the estimation of the gravity of the case does not depend upon the violence of the symptoms. A severe attack is not necessarily serious, nor is the mildest free from danger. The importance of the symptoms must be estimated by an examination of the conditions which have induced the muscular exhaustion. This is, as a rule, not a matter of much difficulty if one searches carefully for a predisposing cause. The age of the patient, the conditions of his or her life, give a guide. If one has reason to suspect that the symptoms have appeared in the early days of advancing senile changes, when the patient, ignoring the limitation of his powers, follows the mode of life pursued in the days of his vigorous manhood, then the probabilities are that with rest and care the heart will recover from its exhaustion and be able to carry on its work for many years in comfort, but at a lower level. The prognosis is most serious where the attacks occur with marked evidence of general arterial and cardiac degeneration, where there is little response to treatment, and where the attacks are induced with very slight provocation. The presence of other phenomena, such as cardiac asthma, pulsus alternans and Cheyne-Stokes breathing, is an additional evidence of such advanced exhaustion that the outlook becomes very grave.

In all cases it is well to suspend judgment until a period of treatment has been tried, the treatment to include the suspension of all forms of effort which predispose to or induce the attacks. This is especially important where there is evidence of a progressive lesion in the heart, as in cases of syphilis affecting the aorta and its valves. If in spite of treatment the attacks recur with little provocation, then the outlook is very serious. Nevertheless there are cases, so severe that for months a patient may scarcely be able to walk across the floor without inducing an attack, where rest for a long period may restore the heart's strength and induce a cessation of the symptoms. A helpful guide is to find out how much a man can do under the most favorable circumstances, even though it may be but rare that he can do so much. If he can at any time walk a few miles, it means that he has still a fair amount of healthy muscle and it is so far a favorable sign.

TREATMENT OF ANGINA PECTORIS

For the purpose of finding a rational therapy, I include under this section all forms of pain and discomfort, such as constriction of the chest, sense of suffocation and sense of impending death, which have their cause in some cardiac condition.

Taking these symptoms as a basis we find they always occur in association with the exhaustion of the heart muscle, whatever may have been the conditions which led to this exhaustion. It is of importance to recognize this relation between angina and exhaustion, for we are at once given a safe guide to treatment, the practical indications being to restore the exhausted muscle and to prevent a recurrence of the exhaustion.

But before dealing more fully with the treatment there is that other factor to be considered—the nervous system. From a variety of unknown causes pain seems to be more readily provoked in some people than in others, as shown by the fact that lesions, apparently identical, give rise to different nervous phenomena in different people. Moreover, as a matter of experience, not only may pain be more readily produced in some people than in others, but when once a tendency to attacks of pain is established the attacks become more easily provoked. The recognition of this helps us in two ways; first, in recognizing the fact that the severity of the pain is no guide to the gravity of the lesion, and secondly, that treatment directed to the nervous system may be of far more benefit than when directed to an evident cardiac lesion. We must, then, in any given case consider not only the cardiac cause of the exhaustion, but also the part played by the nervous system in the production of the symptoms.

In order to find out the best means of treatment we must seek for the cause of the exhaustion. This is not, as a rule, a difficult matter and here I illustrate the manner in which this may be done.

The most common forms of angina appear between the ages of fifty-five and sixty-five, and in these cases we have to consider what may have induced the exhaustion. We know that in many people at this time of life changes take place in the circulatory apparatus which are due to advancing years, aggravated, it may be, by the kind of life that has been followed. We, therefore, carefully inquire into the life history, and may find that the patient has been leading a strenuous life for a great many years, doing as much as when in the prime of health, and thrusting from him the indications which revealed to him signs of heart exhaustion; for if inquiry be made some symptom of discomfort, as a slight tightness across the chest, or breathlessness, has appeared at intervals long before the onset of the pain which forced him to seek advice. Manifestly the exhaustion here has been produced by a long-continued strain, and the possibilities are that, after a period of rest, the heart will regain a measure of strength and the distressing phenomena will disappear. In such cases it is not necessary to stop a business man from doing all his work, for to do so may affect his circumstances most seriously and his business affairs may be unnecessarily jeopardized. It may be quite sufficient for him to omit some of his less pressing duties and the relief, thus obtained, may cause a cessation of the attacks.

As a rule, it is best for him so to arrange his affairs that he can take a restful holiday with his mind at ease. The holiday should be spent in a manner which affords the maximum of enjoyment with the minimum of effort. If the patient has no particular bent and would perhaps find a holiday drag wearily, he might be sent to some watering place and made to undergo the régime peculiar to that place. The carrying out of the directions would give his mind sufficient exercise to prevent tedium, and he would have the opportunity of reaping what benefit the waters may possess. In all cases the mode of living and the habits of the individual must be considered, so that errors in diet, abuse of alcohol or tobacco, may be corrected. There may be some valve defect (an aortic systolic murmur is very frequent) or a high blood pressure, or thickened arteries may be detected. While noting such conditions, treatment should not be directed to their amendment, for they are but associated phenomena and not amenable to treatment.

In cases which do not benefit from such limited restrictions and when the attacks are demonstrably the outcome of an advanced exhaustion of the heart, then more rest is required until, in extreme cases, it is necessary to confine the patient to bed. In the more severe cases strict attention should be paid to the amount and kind of food and the state of the bowels; freedom from annoyance and worry, and a sufficient amount of sleep should be ensured, if necessary, by the use of hypnotics.

It is only in rare cases that, in spite of this line of treatment, the patient gets worse, the attacks recur, and the patient finally succumbs. This resistance to treatment is an important element in prognosis, for it will invariably be found that the lesion which has induced the attacks of angina is of such an advanced nature that it has rendered the heart unfit to maintain a circulation compatible with life. In such cases, when, in spite of rest and the correction of any errors in diet, no progress is made, and the attacks supervene on the slightest exertion, we must recognize that we have to do with an exhaustion so extreme that its cause may be due to organic changes in the heart muscle, and that no prospect of recovery can be entertained. Under these circumstances the patient must be kept at complete rest, his food and habits carefully regulated, and all circumstances likely to induce the attacks of angina avoided, while sedatives, such as chloral or opium, may have to be administered to prevent the occurrence of the attacks or to lessen their frequency.

But before coming to the conclusion that the heart condition is irremediable, we must weigh carefully the possibility of the attacks being more readily provoked in consequence of an exalted susceptibility of the nervous system. In many cases, where the slightest exertion, such as getting out of bed or walking across the floor, may induce an attack, if careful inquiry is made it may be found that the patient has passed through a period of stress, worry, or anxiety, or may have had sleepless nights. If such patients are protected from their worries and acquire peaceful, restful nights, recovery may at once set in and proceed to a surprising extent, even when there is advanced degenerative change in the heart and blood vessels. The most useful remedy in these cases is the bromide of ammonium, given in doses of 1.3 grams (twenty grains) three times a day, until a certain degree of lethargy and drowsiness is produced. This remedy not only induces sleep, but renders the patient more indifferent to the worries and troubles which may beset him. In some cases there are periods when the attacks of angina are liable to recur, and these are preceded by sleepless nights. The administration of the bromide when the sleeplessness first appears may prevent the exhaustion which induces the anginal attacks.

A very important factor has to be considered in treating cases with angina pectoris, as well as all forms of neurotic heart, and that is the mental condition. The fact that patients who suffer from angina pectoris sometimes die suddenly, or die shortly after the appearance of the symptoms, has so impressed the lay mind as well as the medical that a very gloomy view of the condition is taken. As a matter of experience, it is only a very small proportion of the cases, even of those with severe attacks, in which there is cause for immediate concern. The vast majority of patients recover to a very great extent and lead useful lives for an indefinite period. We should, therefore, make a special study of each case, and when we find the condition is not grave a favorable prognosis, given with an air of conviction, will at once do a great deal of good. The element of hope must be based on a clear conception of the heart's condition, and the careful physician will have little difficulty in detecting the essential feature in each case.

In certain cases, where there is aortic valvular disease, attacks of angina pectoris are easily provoked, and the patient's mode of life must be greatly restricted on this account. The attacks may appear in patients between thirty and forty, where the valve disease was due to rheumatism or syphilis, as well as in the elderly, where the lesion may be due to fibrotic degeneration. So severe may these attacks be, and so readily provoked, that patients are forced to lie abed. In such cases relief may be obtained by pushing the bromides, 5 to 7 grams a day (one and a half to two drachms), until a condition of lethargy is produced and the patient lies in a drowsy condition. After a few weeks, if the patient is allowed to come out of the influence of the drug, a distinct improvement may be found. Such a patient is, otherwise, one of the most difficult kind to treat, and is liable to become addicted to the opium habit when opiates are resorted to for relief. Great suffering, however, is consistent with a long life, and I have watched cases of this sort for twenty years.

Treatment During Attacks.—The slighter attacks require no treatment beyond the cessation of the exciting cause (such as effort), but, when they become more severe, rapidly acting vasodilators should be administered, such as hot drinks, hot water with whiskey or brandy, and best and speediest of all, amyl nitrite by inhalation or nitroglycerin. The nitrites are not successful in all cases, but often their action is rapid and the relief is generally complete. When it is successful, it is inferred that the patient has previously had constricted arterioles, or increased arterial pressure, and that the pressure was reduced and the heart was eased. This is, however, not the full explanation. A patient with cardio-sclerosis had an attack of angina pectoris in my consulting room. I took his blood pressure, and found it 190 mm. of mercury and then administered nitrite of amyl; it acted instantaneously and gave him perfect relief. After fifteen minutes I took his blood pressure again, and found that it had risen to 200 mm. of mercury. Though the pressure was higher, he had no pain.

Oxygen inhaled during an attack may give relief. When the nitrites fail to relieve the patient we are forced to use chloroform, chloral, or morphia in doses sufficient to give relief. I have occasionally found that chloral acts beneficially not only in relieving the somewhat long attacks, but in preventing the recurrence of the attacks, particularly when given at night to induce sound sleep, or when there are repeated attacks, chloral in doses of 0.25 to 0.3 gram (four or five grains) given four or five times a day may produce a degree of drowsiness during which the attacks cease.

Toxic Angina

Attacks of pain, sometimes of great severity and alarming in appearance, are very common among women who suffer from debility, chiefly, if not entirely, toxic in origin. These attacks are bewildering in their variety and might be broken up into a great many groups. The more I see of them the less inclined I am to refer attacks of pain in women to a serious condition of the heart. I have laid it down for my own guidance that women who suffer from attacks of angina under fifty years of age with no demonstrable signs of gross disease of the heart (as aortic or mitral valve disease or great enlargement) suffer not from a primary heart trouble but from some condition which produces general exhaustion, and the heart pain is but the expression of the heart exhaustion and serves as an indication to search elsewhere for the cause of the trouble. I explained this view to a colleague one day, and he said that he remembered in his boyhood that his mother when between forty-five and fifty years of age suffered from attacks of angina pectoris of such severity that her life was despaired of, but she had died at the age of ninety-four.

The circumstances which provoke the condition are described under exhaustion, where it will be shown that, during and after some infective process, the circulatory and nervous systems are often temporarily affected. The cardiac manifestations are variable, palpitation and breathlessness being frequent signs, while pain and other sensory disturbances are very frequent. It is necessary to enter upon a description of these, as frequently they are taken as evidence of serious heart trouble.

The sensory disturbances arising in a toxic heart may be limited to a slight aching over the left breast, with or without a small area of cutaneous hyperalgesia, or there may be pain of the most agonizing description and a widespread field of cutaneous hyperalgesia.

Many women complain of an aching in the left breast and pain on pressure, and some may consult the doctor in the fear that these are signs of a cancer in the breast. This pain and aching may be very distressing, lasting for hours, never attaining to a great severity, but sufficient to cause such suffering and discomfort that their lives are rendered miserable. This happens particularly among hard-worked women with a large family or other dependents who require attention during the night so that the woman's sleep is broken and disturbed.

The pain may appear only at periodic intervals, and be of an agonizing description and indistinguishable from attacks of angina due to grave disease of the heart. If the doctor takes into consideration only the attacks of pain, he is liable to be misled. If, however, he recognizes that the patient is a woman under fifty, and there is no gross disease of the heart, he will see the necessity for seeking for some cause of illness in other regions of the body. The most common cause for this condition is found in the intestinal tract.

If careful examination be made of the abdomen, an area of hyperalgesia of the skin or deeper structure will often be found, while a resistance, sometimes slight, but quite distinct, may be found in the muscles of one side of the abdomen. A history of constipation can frequently be elicited, and although the patients may declare that there is no constipation, yet they will frequently admit that they have been conscious of slight pain and tenderness in some part of the abdomen, usually in the right iliac region, and they may say they have had attacks of appendicitis. In the few cases that have been operated upon at my recommendation, there was found in all a great many adhesions around the cecum. An inquiry in which I am at present engaged reveals that adhesions here and in other parts of the intestinal tract are exceedingly common, and are associated with or caused by stasis and decomposition of the intestinal contents. Poisoning from other sources may give rise to very alarming symptoms, as an accumulation of pus in some cavity such as the antrum, or an abscess in the pelvis or elsewhere.

While the character of an attack may resemble the attacks occurring in men with disease of the heart, the manner of onset is usually different. It may occur when the patient is at rest, or on the slightest effort, while at other times the patient may undertake considerable effort with no distress. An inquiry into the previous history of the patient, particularly with reference to the state of health in which the patient had been before the attacks appeared, will afford ground for forming a safe opinion as to the gravity or absence of gravity in this kind of case.

Another feature is that the pain is frequently not limited to the well-defined area as shown in Fig. 3, but may spread or be described as spreading around the whole arm and down into the abdomen. Indeed, the distribution of pain is like that of hysteria, and many of these cases are described as hysterical angina, pseudo-angina or mock angina, and in consequence the patients' complaints are treated rather lightly, particularly in view of the fact that none ever shows other signs of serious heart trouble. But this view of the matter is not quite justified, for I have repeatedly found patients labelled as hysterical or neurasthenic or hypochondriacal, who were really in a poor state of health and suffering from some form of toxemia, frequently intestinal. The absorption of decomposing products from the intestine has an injurious influence upon the central nervous system, and to pass these serious manifestations by as merely hysterical is to misinterpret their significance.

Many men who have been exposed to toxic influences (microbic infection) and have been exposed to severe bodily fatigue develop similar symptoms. Thus among soldiers exhaustion of the heart with pain and other sensory disturbance is not an infrequent occurrence. Among these toxic cases are a number which have been described as vasomotor angina pectoris, due to the fact that there is marked evidence of a contraction of the peripheral vessels. I have already dwelt upon this feature in angina pectoris in cases of arotic regurgitation, but these toxic cases are of a different type, although they have been mixed by some writers. The idea that vasoconstriction is a common cause of angina pectoris has gained ground, but as a matter of fact, it is of rare occurrence, and certainly not the cause in the majority of cases.

Many patients who suffer from angina pectoris experience an attack when they go into the cold air. In them there are some organic changes in the heart and the increased peripheral resistance caused by the cold embarrasses and exhausts the heart, or a constriction of the arterioles, similar to what takes place in the skin, may occur in the heart. But there are rare cases in which the cold may induce such vasoconstriction that pain may occur in patients who do not suffer from gross disease of the heart, but from a toxic condition. Thus a patient, aged thirty, whom I had under observation for a number of years, complained of the miserable sensation of exhaustion and chilliness which she experienced during cold weather. On a few occasions, she suffered from attacks of pain in the chest, of which the following is an example. On a raw November Sunday morning she went to teach in a Sunday school. The room was cold and she felt chilly. Still feeling chilly, she went to church, a cold damp building. The sensation of cold got worse, and towards the end of the service she began to feel a pain in her left chest. This pain increased, and on reaching home it became of great severity and extended from her left chest down her left arm. She was put to bed with hot bottles and given hot drinks, and when she became warm the pain subsided. By taking precaution she did not have any more attacks.

Prognosis.—I have never seen a patient of this type suffer from any grave signs of heart failure, although many live invalid lives for years, due to the primary disease. The outlook, therefore, depends on the possibility of the removal of this primary cause, which, if accomplished, is speedily followed by recovery. Otherwise the impaired health may persist for many years, though some regain a wonderful degree of health after sixty years of age.

Treatment of Toxic Angina.—Recognizing the nature of the trouble, the treatment is naturally directed to removing the cause of the impaired health, and for this purpose a search must be made. Even when not apparent at first the doctor should always be on the outlook for some source of infection, and not infrequently some new development of signs will reveal the source though it may be after months or years.

In addition to attending to sensible lines of managing the patient for the impaired health, special lines of treatment may be required for the heart. This is attained best by protecting the heart from exertion beyond that which it can accomplish in comfort, as by diminishing the amount of bodily effort and by securing sleep. There are periods when the pain becomes easily provoked, and besides rest at these times bromide of ammonia, pushed until it produces a slight degree of drowsiness, is often very beneficial. When the patient feels this drowsiness, then the drug should be stopped, and resumed from time to time when the suffering calls for relief. In this way the patients get to know when the medicine is required and can obtain relief until such time as the health is improved. There is no fear of the drug habit being acquired, as no patient ever has a craving for the bromides.

Exhaustion, Palpitation, and Syncope

There are a number of people who suffer in many ways in whom one or more of the dominant symptoms are cardiac in origin, and as a consequence these are often looked upon as cardiac patients and treatment is devoted to the heart, while the trouble is really of a general kind and the heart condition is but a portion of a state in which most of the organs participate. In producing this state, a variety of circumstances take part, the most common being some toxic condition which lowers the vitality, as microbe infection, or a chronic affection of other organs. Superadded there may be persistent overwork, worry, sleeplessness, and insufficient nourishment. This subject is a large one and here I deal briefly with only a few of its more common aspects as they affect the organs of circulation, namely, with the symptoms of exhaustion, palpitation, and syncope.

Exhaustion

When exertion is made, as in walking, many people become conscious of a sense of weakness, which causes them to desist. The sensation is difficult to describe, though most know from personal experience what the feeling is. The chief element is a strong desire to stop and sit or lie down, the legs feeling limp and powerless. If the exertion has not been carried to an extreme degree, the sensation quickly disappears when sitting or lying. If exertion be persisted in, the sensation may pass off in milder cases, while in severer cases the individual may stagger and fall, and even lose consciousness.

Accompanying the feeling, other symptoms may be present, as breathlessness, palpitation, and pain over the left chest, sometimes slight, sometimes severe. When these signs are present, the patient associates the condition with the heart, and the doctor may refer the whole train of symptoms to this organ, particularly if there be present some abnormality or seeming abnormality, as an undue increase in rate, an irregularity, a murmur, or slight increase in size. It is because of this misconception that I deal with the matter, for the sensation is not primarily a cardiac one, though the heart may participate in the general weakness, of which the exhaustion is the sign. To bring out clearly its salient characteristics, and how it differs from the symptoms peculiar to heart exhaustion, certain of its features should be considered. The sensation is usually not constant. If provoked by exertion, it will be found to vary from day to day, or there may be periods of weeks when the patient is free from it, and then weeks when it is easily provoked. Some days, if the patient walks a short distance, as on a hot and close day, too heavily clad, the sensation is readily provoked; on other days, when the sun is bright, the air cool, and the individual lightly clad, a wonderful amount of exercise may be taken without discomfort. Certain other states besides exertion may bring it on, as standing in a warm room. Many women feel faint and exhausted when having a dress fitted, or on raising their hands above their heads while standing and arranging their hair.

To appreciate the nature of this condition it is necessary to search for other signs. In many of those people who suffer from periods of exhaustion we find other abnormal signs referable to the vasomotor system. Thus, many will show changes in the peripheral circulation, the hands and feet often becoming cold, not only in cold weather, but in response to some mental stimulus, such as the excitement of being examined. Many shudder at the idea of a cold bath, as the after-reaction is one not of a warm congenial glow but of a shriveled-up, cold feeling. In some the fingers become pale and cold, and the sensibility of the fingers will be so diminished that the fingers are numb. At other times, the hands and nose become red. Some, in a warm atmosphere, become flushed and disagreeably hot. Not infrequently, pressure applied to the abdomen will cause the jugular veins to become full (see Fig. 5). The blood pressure in these cases is usually rather low, particularly during the attacks of exhaustion. It may rise as soon as the patient lies down or after the exhaustion passes off, and this accounts, probably, for the fact that sitting or lying speedily dissipates the sense of exhaustion.

Taking all these facts into consideration, I think we are justified in referring the state of exhaustion to a depletion of the higher nervous centers. The vasomotor system is oversusceptible to stimulation, in the one case producing an overaction, a contraction of the vessels in response to cold, in the other case a widening of the peripheral field from warmth or exertion. In many cases the wearing of an abdominal belt that firmly grasps the abdomen, will prevent the attacks of exhaustion and faintness.

The heart is often irritable and causes a good deal of distress from attacks of palpitation, or from extrasystoles. In some it may dilate and even show signs of insufficiency in the sense that effort may readily produce distress or discomfort from breathlessness or palpitation. The mental condition may be affected; irritability of temper and depression are not uncommon. In many nutrition is impaired, and these people become spare and thin. The skin becomes dirty and yellow, especially in the armpits and over the abdomen.

It is not always easy to find the real cause of this condition, although I think there is now enough evidence to show that, in many cases, it is due to some toxic influence. A very considerable proportion of those who suffer so readily from exhaustion have distinct evidence of gastrointestinal troubles. Many complain of different signs of dyspepsia, and we can often detect evidence of stasis in some portion of the intestinal tract, even when there is no complaint made by the patient of indigestion. Constipation is often present. Many years ago I was struck by the disappearance of those characteristic vasomotor phenomena (cold hands and feet) in a man with a chronic duodenal ulcer, on whom a gastroenterostomy had been performed.

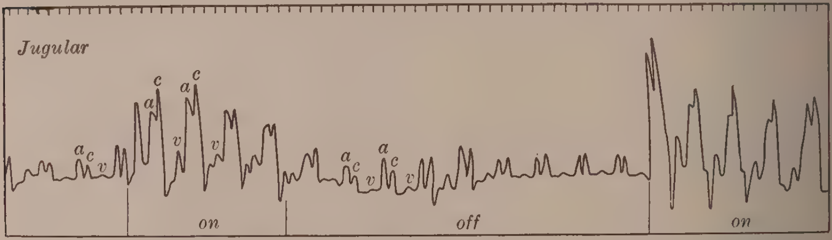

Fig. 5.—Tracing of the jugular pulsation when pressure is applied to the abdomen (*on*)—the jugular vein increases in size; when the pressure is removed (*off*)—the venous distension diminishes.

Although the absorption of the products of decomposition from the intestines is probably the most common cause, absorption from other centers of infection is possible, as from the teeth and obscure inflammatory conditions, like chronic appendicitis. A typical form is seen after exhausting illnesses, such as typhoid fever or influenza. In fact any prolonged bacterial infection may give rise to it.

Palpitation

The term palpitation is usually employed in a somewhat loose sense by patient and doctor. As it is perceived by the patient and recognized as being due to some disturbed action of the heart, it is only by intelligently questioning the patient that we can get the knowledge necessary to understand its nature, except in those cases where we see the patient during an attack. The doctor interpreting the description given by the patient may bring out the fact that the condition is due to some abnormal rhythm, as extrasystoles, or auricular fibrillation, subjects dealt with elsewhere. The examination may bring out the fact that the heart beats heavily, forcibly, regularly, with little or no increase in rate, or with a considerable increase in rate, and it is to these states I would restrict the terms palpitation, and to which the following description refers.

Palpitation may occur in relation to a great variety of complaints. The patient is usually conscious of the change in the heart's action; he feels the rapid beats and sometimes describes them as "gentle," sometimes as "hard and hammering." This latter sensation may occur with little or no increase in frequency. In cases of valvular disease, where there is a limitation of reserve force, slight physical effort or mental excitement may readily induce an attack. Even in the healthy certain mental states may have the same effect. When the system is weakened from disease, the liability to attack is naturally much increased. It is in certain neurotic subjects, particularly females, that one sees the complaint attain its most distinctive features. There may be no organic affection of the heart; and though frequent attacks may ultimately induce exhaustion of the reserve force, yet as a rule they do not appreciably shorten life. Anything that startles the patient, whether it be a sudden noise, or mental perturbation, or uncomfortable dreams, readily induces an attack. But an attack may supervene as the result of more obscure causes, amongst which may be included reflexes from organs more or less remotely situated (stomach, uterus); the source of the trouble may in other cases be indiscernible.

When a severe attack comes on, the patients may become painfully aware of the violent action of their heart. They prefer to sit upright; they draw deep inspirations and move uneasily from side to side, with the hand pressed over the heart. The attack is accompanied by sensations of a distressing nature, such as a sense of suffocation and a fear of impending dissolution. When it subsides it leaves the patient exhausted.

During the attack the pulse is usually increased in frequency. The artery may be of fair size; sometimes, however, it is very small. The impact of the pulse wave on the finger is sudden and sharp, and of extremely brief duration.

We occasionally meet with patients in whom the pulse is extremely rapid for a period, sometimes for a few minutes, sometimes for a few hours, but who experience no sensation other than exhaustion, and the attack quietly subsides. The causes of these attacks are so obscure that it would be mere guesswork, in the majority of cases, to discuss them. In patients with a high blood pressure attacks of palpitation at odd times, as in bed, or on exertion, or excitement, are not infrequent.

The opinion given by the doctor about these cases should be based, in every instance, on careful consideration of the cause of the irritation of the heart; and inquiry must, therefore, be made into the patient's state of health and into the consideration of other organs, particularly those of the digestive system. The treatment is directed to the removal of any exciting cause or to the improvement of the patient's health as a whole. Where the patient is of a nervous temperament, or where there is high blood pressure, the judicious use of the bromides will help in diminishing the frequency and severity of the attacks, especially of those attacks which occur in the night. During the attacks relief is often obtained by drinking a cup of strong hot coffee or tea.

SYNCOPE

Many people when placed under certain circumstances suffer from a diminished supply of blood to the brain, and as a consequence the patients become limp, and unconsciousness may result. This may result from the action of the heart being depressed by excess of vagal influence, or from the stagnation of a large quantity of blood in the large abdominal veins. Abnormal actions of the heart, as in the standstill of heart block, or in the diminished output with greatly increased rate of auricular flutter, may produce such a degree of cerebral anemia that unconsciousness results. These abnormal actions are dealt with elsewhere; here the syncope due to vagal action and venous stasis will be considered.

Syncope from Vagal Stimulation.—When an impression is made by means of a violent mental stimulus, for example, alarming information or the sight of some harrowing scene, a syncope may follow; again, violent intestinal peristalsis, or severe pain, as for example that attending the opening of an abscess, may produce syncope. The patient becomes pale, beads of sweat may break out on the face and the whole body perspires, and as recovery takes place the patient may vomit. The pulse in such cases may become infrequent and of very low tension. Sometimes after recovery the patient may pass a large loose movement, indicating that the attack was probably the result of an intestinal stimulation.

Syncope from Venous Stasis.—Many young people faint when standing in a close atmosphere, *e. g.* schoolboys attending chapel; many women of anemic, flabby habit faint under similar circumstances; soldiers on the march, especially in hot weather, faint, probably because their heavy clothing keeps their bodies so warm that the peripheral vessels are dilated to such an extent that they deplete the brain. In some people the tendency of the blood to drain into the large abdominal veins is so marked that the fainting attacks are easily produced. Some of these people can be recognized by the fact that if pressure with the flat of the hand is applied over the abdomen when the patient is lying down the jugular veins will be seen to swell up. (Fig. 5.) This is an undoubted sign of the overfilling of the large abdominal veins, as the pressure on them fills the right heart and the blood flow in the jugular veins is impeded. In healthy people one gets no such reaction, or only a very slight one, while in those in whom the exhaustion is easily provoked, the swelling of the jugular vein on pressure of the abdomen is sometimes very great. I have seen one man in whom this tendency to exhaustion and giddiness was so great that he could not follow his work and was only comfortable when lying down. A few minutes after standing up the heart raced off at a great rate and he became giddy and faint. A firm abdominal belt at once produced such relief that, so long as he wore it, he was able to work. Another man who consulted me staggered and reeled and sometimes fell on standing up. He had made a habit of bending down and squeezing his belly before standing up. I found that the pressure in the abdomen caused great fullness of the jugular veins.

Syncope from these two causes occurs without any disease of the heart and the prognosis depends on other conditions which are present, generally of a kind that tend to weaken the whole system. While treatment should be employed to remove causes that tend to produce debility and to brace up the system by suitable measures, much help may be afforded in those cases with stasis by exercises that strengthen the abdominal muscles and by the use of a suitable abdominal belt that can be adjusted so as to give a support without interfering with the free movements of the body.

The Soldier's Heart

Exposure and fatigue during the war have impaired the health of many of the soldiers, and among their ailments are symptoms which are generally attributed to affections of some part of the circulatory system. While these conditions are not distinctive, being indeed such as are common in civil life, yet on account of the number that are affected, and because of the difficulty in recognizing the nature of the trouble, I give here a short chapter dealing with my own observations on the matter and the conclusions drawn therefrom, which practically agree with the experiences of others who have made a special study of the subject. In this reference to the soldier's heart I do not deal with the cases in which there was manifest disease of the heart, as the principles of diagnosis and treatment in them are the same as in civil life.

The description given of exhaustion corresponds to the symptoms present in the condition described as "soldier's heart," or the "irritable heart of soldiers." The British Government, in 1864, appointed a committee to inquire into the heart condition of soldiers, as the condition we recognize today was the cause of much discussion at that time. During the American Civil War the surgeons had ample experience of this trouble, and articles published by Hartshorne and Da Costa are almost identical with the description which is given by the army doctors during the present war. The subject was one that had interested me for many years, and when the war broke out I seized the opportunity of making myself personally acquainted with the condition.

In soldiers invalided because of heart trouble, we find a good deal of variation in their appearance and symptoms. The face is often lined and drawn; many are spare and thin with a great vasomotor instability, as shown by the manner in which the peripheral circulation varies, the hands and fingers at times going pale and cold, at other times the fingers are thick and red, and the nose likewise becomes red and even blue with slight exposure to cold. If they have been treated for some months by rest and feeding, some become pale, fat, and scant of breath.

The chief complaint is an absence of the feeling of being well; they often feel out of sorts and a sense of fatigue or exhaustion easily induced is common to all. Breathlessness on moderate exertion is frequent, and more frequent is pain over the region of the heart. The physical signs are variable. The heart's rate is often not increased; in some it is persistently increased, as frequent as 120 per minute. More frequently, at rest, the rate may be quite moderate, but exertion, sometimes slight, may produce an undue rapidity.

Murmurs, systolic in time and heard in different regions, are frequent, while an increase in size, usually slight, is not uncommon. In a few cases there is a slight edema of the legs.

The mental condition is somewhat varied. Periods of depression are not infrequent, and the patients are often very irritable. They accept the view that they have something wrong with their hearts and readily yield to all restrictions, and are often content to lie in bed and brood over their woes. These are the salient features in a great majority of cases. We find identical conditions in people recovering from an exhausting illness, as typhoid fever, or after a severe surgical operation. We see all these phenomena well marked in people who are suffering from some microbic infection, and we also find them in people who have suffered a long mental and physical strain, particularly with insufficient sleep.

The account given of the onset of symptoms is peculiarly instructive. Some will say they were in the trenches and felt well and fit until one day they felt seedy and ill, and this continued until they were compelled to seek medical advice, when they were found to have a raised temperature. A few days' relief was obtained, and they returned to their work still feeling far from well, and after a few weeks of the strenuous life in the trenches they collapsed, sometimes with loss of consciousness, breathlessness, or even pain.

The nature of the predisposing illness varies. Sometimes it is an attack of diarrhea, which persists for a time; sometimes it is after a definite illness, as measles, but most give a history which we can safely surmise as being due to an infection. In a few cases one cannot get such a definite account of the starting of the illness, but many do recognize the gradual onset of the trouble. That is the story of the majority of cases, but there are a number from whom we can get no suspicious history of infection, but where there is an account of a very strenuous life.

To grasp fully how this exhaustion is brought about, we must understand the life in the trenches. The story of some of these soldiers is illuminating. One, in December, 1914, suffered from appendicitis and was operated on. He returned to duty three months after, and in June went to the front. Immediately on arrival he went into the trenches and was there a fortnight. Every night was spent in repairing the damaged parapets. They were constantly being shelled. He never slept at night and often only got a few hours' sleep in the day, often being twenty-four hours without sleep. One day a shell exploded in the trench, knocking him partly unconscious. On regaining consciousness he stuck to his work for twenty-four hours, but had to give in, feeling weak and ill with pain over the region of the heart.

Effects of Strain During Infection.—So great is the mental strain and bodily exertion with sleepless days and nights while the trenches are frequently bombarded, that one might be disposed to consider that these factors would be sufficient to account for all the symptoms. But we find identical symptoms present in many who have never been to the front, and who have had no excessive bodily or mental strain, but who have suffered from some febrile infection. The majority also, as I have said, give a history of some previous illness, and it is necessary that we should recognize the effects of strain or effort complicated by febrile illness. For that purpose I recite the following experience.

A young officer was training for a foot race, and every day spent some time running round a track. One day while doing this, he collapsed, fell, and was picked up partly unconscious. A doctor was summoned, who said he had strained and dilated his heart and that was the cause of his collapse. I was asked to see him, and, after getting this account, I recognized that a man who had taken a considerable amount of exercise the day before could not possibly suffer from heart failure, so I asked him if he felt quite well before he began to run, and he admitted that he felt rather seedy, but hoped to shake off the feeling with the exercise. The temperature was taken and found to be raised a few degrees, so I had no hesitation in stating that the cause of collapse was the toxic influence of some microbe invasion and that after the subsidence of the fever and a few days' rest, he would be all right. That is what happened, and he was able to resume his training and ultimately ran his race in perfect health.

The action of toxins produced in the body by bacterial invasions has not yet been clearly worked out, but so far as I have gone into the matter a clear and distinct group of illnesses can be attributed to the toxins, even when the organisms themselves do little damage. The phenomena I have described as characteristic of the soldier's heart give the idea of the point I want to establish, that the condition is one of general exhaustion, and the circulatory symptoms are but parts of a general manifestation. Many people who ultimately develop some definite illness like consumption suffer in similar manner, and the reason is probably the same, a sense of weakness and ill health due to the invasion of the body by the tubercle bacillus, before any physical sign is produced. It is just possible that in some of these cases there is an actual invasion of the heart by some microbe and these symptoms may be the precursor of a chronic myocarditis, but so far this matter is but a surmise.

Treatment of Soldier's Heart

If we recognize the nature of the illness from which these soldiers suffer, we can readily see on what principles treatment should be based. The lines are those we employ in civil practice. If the patient be the host of some microbe, the treatment should be devoted to increasing his power of resistance. If he be poisoned, treatment should be devoted to the elimination of the poison. Should certain tissues be injured by the invading microbe, or by the toxin, or by physical strain, then treatment should be devoted to their healthy renewal.

These indications are practically those which should guide us in treating individuals after an exhausting illness. We have, however, in addition, to consider the mental condition of the soldier whose experiences have depressed his mental faculties, and who has been told he has some heart trouble. This knowledge always tends to depress and to make them extremely amenable to that form of treatment that is the worst for them, rest in bed or the avoidance of exertion. If we recognize that such cardiac phenomena as murmurs, increase in size, and variability of rate are but the manifestations of an irritated heart, we shall see that too much rest is not beneficial. Every organ benefits by the judicious exercise of its functions, and the heart can also be beneficially stimulated.

The principles of treatment, then, should be devoted to increasing the health of the body as a whole in such a way as to increase the natural resistance to infection, to eliminate toxic influences, and brace up the whole man bodily and mentally. The best way to achieve this is by fresh air and judicious exercise in the fresh air. I need not labor the fresh-air idea, as it is evident to all, but I want to emphasize the question of exercise.

There is a notion deeply rooted that, if there is anything wrong with the heart, the patient must be restricted in the amount of effort, and medical men who are themselves afflicted are quite content to lie in bed or move gingerly about. The line I have adopted is to reassure the patients. They often feel miserable, so that there is a mental side to the case, which is aggravated by the supposition that there is something amiss with the heart. This aspect of the case has to be met, and consequently in our treatment this view has to be kept in mind.

When all fever has subsided, or when there is but an occasional rise of temperature, I encourage the patient to get up and go about. I find out the form of outdoor exercise which gives him most pleasure, so I recommend to him to start as soon as possible any form of sport or game which he can get: fishing, riding, shooting, golf, etc.

In recommending such exercise I have two objects in view. The first is the mental condition of the patient, and I need not insist upon the beneficial effects of occupation. The more interesting that is, the more likely is the patient to be taken out of himself. I have referred to the fact that the sense of exhaustion is the predominant symptom in these cases, and that it is probably vasomotor in origin, due to the irritation of the central nervous system. We know that the mental state may play a part in producing exhaustion, for we find that a boring form of exercise will readily produce it, while a form of exercise that is full of interest can be borne for long periods without any exhaustion. Therefore, this out-of-door occupation should be in an attractive form.

In recommending effort, I know it will be said that there is danger in this, particularly when such physical signs as murmurs and dilatation are present. If the true nature of these signs be recognized, that they are but the expression of a temporary enfeeblement of the heart muscle, and that the same measure for restoring a flabby leg muscle applies to a flabby heart muscle, we shall see the importance of exercise judiciously employed. No doubt injudicious exercise may do harm, but there is one precaution of a very simple kind which suffices to prevent any danger, and that is to instruct the patient to indulge in his exercise so long as it gives him pleasure and causes no distress nor discomfort, but to stop or slow down as soon as he experiences a sense of exhaustion, breathlessness or pain.

This simple and easily comprehended dictum contains in it the whole philosophy of the therapeutics of exercise as applied to the heart, and may be used with safety in all obscure and doubtful conditions of heart weakness.

Mechanical Aids in the Examination of the Heart

A conception has arisen among experienced clinicians that the limits of clinical examination by the unaided senses have been reached and that, if advance in medicine is to continue, new methods of examination must be devised. They turn hopefully to the workers in other fields of medicine, particularly to the laboratory worker and to the exponents of other sciences, and these have responded to the call, and there are now a great number of methods of examination which are employed as aids to the senses or as substitutes for them.

A great deal of light has been thrown upon many obscure problems by the use of mechanical devices and other laboratory methods, and this has strengthened the view that it is only by such methods that progress can now be made. The employment of instruments of precision fosters the idea that medicine is becoming more scientific with the extension of their use, and there is a tendency to rely more and more upon them, and to substitute them for the senses of the physician. I have little hesitation in saying that this attitude towards methods of examination, which is dominant to-day, is based on a fallacy, and so far from the clinical methods of examination by the unaided senses being exhausted, they have not been sufficiently cultivated, and the substitution of mechanical methods for them shows a lack of understanding of what clinical medicine means and how its study should be presented. If the reader will refer to the classification of symptoms given at the beginning of this article he will find that it is absolutely necessary, in dealing with diseases of an organ, to appreciate the functional efficiency of an organ, and that there are symptoms which reveal this. He will, however, understand that the symptoms revealed by mechanical device cannot do this, for they all belong to the structural group. This consideration reveals where the fallacy lies and shows that instruments can never supersede the intelligent employment of the senses.

If we take the first of these instruments devised to aid in clinical examination, the stethoscope, we will see that the failure to realize the nature of the information it reveals has led the profession astray.

About a hundred years ago auscultation began to be systematically employed in the examination of the heart. With that injudicious enthusiasm which at all times has heralded a new method of observation, fabulous qualities were at first attributed to the stethoscope. People were found to have murmurs before their death; hence, before any single observer had watched individual cases long enough to understand the significance of the murmurs, the statement went forth with all the weight of the highest authorities that these signs betoken grievous heart trouble. Today, notwithstanding the enormous amount of attention which has been given to the subject, the whole profession suffers from this untrustworthy observation. Perfectly healthy men are rejected for the army, or invalided out of it, because a murmur has been detected in their hearts. Others, who present themselves for life insurance, are rejected or made to pay a higher premium for the same reason, while innumerable individuals are subjected to prolonged treatment and great restrictions in their mode of life because these early superficial observations have misled the profession. At times, physicians of experience will admit that certain murmurs may not have a serious significance; in saying this many of them appear to imagine that they have made an important contribution to the subject. But having failed to point out at the same time how a murmur can be valued so as to discover when it is of significance and when it is not, they have really failed to carry forward our knowledge in any respect. The result of this imperfect comprehension of its meaning is that, at present, every graduate leaves the hospital with but the vaguest notion how to assess the value of a murmur. This confusion has arisen from the fact that the profession had not realized how the clinical value of murmurs should be assessed, and in their confusion they turned their attention to devising new stethoscopes. Thus we find for a great many years attempts were made in this direction, and even today the process goes on as shown by the introduction of the box-stethoscope. The result of all this expenditure of energy is that in essentials the knowledge of auscultation has made little progress during the last fifty years, and what progress has been made, has been by employing methods peculiar to clinical medicine and by using the simplest instrument, the wooden stethoscope, which indeed can scarcely be called an instrument, as it is simply interposed between the chest wall of the patient and the physician's ear for the reason of cleanliness and convenience.

In this account of the history of the stethoscope is seen the reason why the progress of medicine is hampered, namely, that it has not been understood how to employ methods in such a manner that will reveal matters essential to clinical medicine. Instead of finding out the bearing that the cause of a murmur or a modified sound had on the patient's future, the energies of the investigator were spent on modifying the instrument. It is as if a poorly nourished individual was treated by modifying the spoon with which he was fed in place of improving the quality of his food. This matter lies at the root of all investigation of medicine, and it depends on the fact that for the advance of medicine methods are necessary which are peculiar to medicine. No one, however skilled he may be in other sciences, or in limited sections of medicine itself, can understand or apply the principles essential to clinical medicine. What these principles are can be found out by finding an answer to the question, "what effect has the cause of an abnormal sign on the patient's future?" To answer this question the physician has to watch the patient through the later years of his life, as well as to search for the onset of the abnormal sign. This necessitates opportunities which are denied those who limit their observation to the study of disease in laboratories, hospital wards, and the post-mortem room. In thus watching the patient, other methods peculiar to clinical medicine must be employed. In every case of impaired health a variety of symptoms is produced, not only by the organ affected by the original disease, but by the effect of the functional derangement of the diseased organ on other organs of the body. We have, therefore, to employ the "law of associated phenomena" in determining the significance of any abnormal sign. The importance of this law and how it can be applied was demonstrated in the description of the manner of estimating the functional efficiency of the heart.

To employ this method of examination requires, not a series of ingenious mechanical devices, but a skilled physician who has obtained from experience a knowledge of the mechanism by which abnormal signs are produced, a knowledge of what will happen to the patient if the cause of the abnormal signs is left untreated, or whether it is amenable to treatment, and this knowledge can only be acquired by a training of the senses.

Another outcome of applying the law of associated phenomena is that on the discovery of a mechanical method the senses should be trained to supersede the use of the instrument in place of the instrument becoming a substitute for the senses. This can be accomplished by recognizing the fact that an abnormal sign is usually perceptible in different ways. Thus an irregular heart recognized by graphic or electrocardiographic methods can also be detected by the peculiar sounds of the heart revealed by the trained ear or by the beat of the pulse revealed by the trained finger or by the movement of the veins of the neck revealed by the trained eye or by all three combined. While the nature of the irregularity was clearly revealed in the first instance by an instrument, the systematic correlation of the signs revealed by the unaided but trained senses allows the instrument to be dispensed with.

In like manner the trained finger can estimate the character of the radial pulse and can give a better knowledge of essential matters than any blood-pressure instrument or sphygmograph. The inspection and palpation of the movements of the heart and the percussion of the heart's dullness give a far more valuable indication of the size of the different chambers of the heart than an X-ray examination. Indeed, I am doubtful if an X-ray examination of the heart has ever thrown the slightest light on any cardiac condition. That the X-rays may reveal aneurysms and tumors, not perceptible to the unaided senses, is no doubt true, but so far as the heart itself is concerned, while it may give a more accurate conception of the size of the heart in bulk, it gives no idea of the particular parts that are increased in size. Like the modification of the stethoscope, the modification of the X-ray methods by orthodiagraphy and teleroentgenography has been of little practical use.

I am not in any sense decrying the use of instruments of precision. What I wish to point out is that they have but a limited sphere of usefulness in the examination of patients. The nature of the knowledge they reveal has been misunderstood, for we can now see the blunders that arose from attaching to the modified sounds of the heart a significance they never possessed, and the same untrustworthy method of estimating the significance of signs revealed by instruments is prevalent today amongst those who place their trust in their use.

The place these instruments should occupy is for the detection of obscure signs. The physician should then search for the associated phenomena that can reveal those signs by the unaided senses, so that these methods are useful in the education of the physician. Then they may be used when necessary for demonstration purposes, to present to the student an appearance by which he can verify the results of his examination by the unaided senses. They are also of use for purposes of research where obscure signs may be revealed and the progress of disease, or the effects of treatment, can be studied.

It will thus be seen that for the routine examination of patients the trained physician rarely needs any of these instrumental methods. The essential features of a cardiac case can be made out by simple means, as by the intelligent questioning of the patient and by the use of his unaided senses in a physical examination. In fact, when one finds a physician employing a series of instruments for the examination of his patients, it may be taken for granted that he is in a rudimentary state of development and his powers of observation are likely to deteriorate for the lack of intelligent exercise of his unaided senses.

As an illustration of the limited and misleading information given by those who place their faith in instruments, the following is an example of great numbers of reports I have seen. The patient consulted me four years before because he had been alarmed by several doctors gravely shaking their heads over a murmur they had detected. The man was fifty-six years of age, and had led a very strenuous life, and his appearance, though healthy, showed the outward signs of advancing years, gray hairs and lined face. He was, however, active and vigorous and capable of taking plenty of exercise without discomfort. The increased size of his heart and systolic murmur were manifestly due to changes occurring with the progress of years, as indicated in Chapter III, so I reassured him. He kept well, leading an active and energetic life till he was again advised to have his heart examined by the "newer" methods. The following is the report sent to the doctor by the specialist who examined him. It will be seen that no reference is made to the amount of effort the heart can stand and there is no estimate of the functional efficiency of the heart, the most important of all matters in the examination, while references are made to electrocardiographic appearances, whose mechanism and prognostic significance nobody understands. The use of such jargon only bewilders the doctor and impresses or alarms the patient.

"Pulse 92 per minute, of normal volume, and regular in rhythm; no evidence of thickening of the vessel wall; systolic blood pressure rather raised for his age, being 162 mm.; on percussion left border of the heart about in the nipple line; a well-marked systolic murmur audible over the whole precordium and in the axilla, its point of maximum intensity being at the apex.

"X-ray examination of the heart shows the organ to be very horizontally placed, left border one-quarter of an inch outside the nipple line, and transverse measurement at least seven inches, thus, considerably enlarged; considering the age and build the aortic shadow is normal, transverse measurement being two and three-quarters to three inches. The electrocardiogram shows left-sided preponderance, poor T deflections, and inverted P's in Lead III.

"The poorness of the T waves indicates that the end of the ventricular contraction is not strong. Considering how very horizontally the heart is placed, I do not think the inversion of the P deflections is of any pathological significance. In my opinion, the organ is somewhat impaired, and the affection is myocardial, in all probability the result of the attack of pneumonia during youth."

The Modifications of the Sounds of the Heart

Although I have already commented on the manner in which auscultation was employed when the stethoscope was first introduced, the universal misconception of its use requires that attention should be called to the nature of information which auscultation reveals.

Within a few years of the discovery of the stethoscope, it was found that people who died from heart failure often exhibited murmurs of different kinds, and hence it occurred to the physician of that day that murmurs were manifestations of diseases of a serious nature. This notion was taught at a period when the cause of the sounds of the heart, and much less the cause of the murmurs, was not understood. As years went on, and investigation into the sounds of the heart ultimately brought out the true origin of some of these, the inquiry into the cause of the different murmurs was diligently pursued, and their origin at the different orifices gradually established. Time after time, physicians were able to indicate at which orifice a murmur was generated, and confirmation of their predictions was found repeatedly at the post-mortem examination. It came to be looked on by the profession that murmurs were an evidence of disease of the valves. As, however, many cases showed murmurs during life, particularly systolic murmurs, and the valves were found intact at the post-mortem examination, a "functional" murmur was recognized. But although these functional murmurs were not considered evidence of disease, they came to be regarded as evidence of impairment of the heart's efficiency, and as such to be indications for treatment and a restriction of the life of the individual.

So deep an impression have modified sounds and murmurs made in the minds of the profession that a large proportion deem them invariably an evidence of an unhealthy heart; the result of which is that we find every form of murmur looked on as an evidence of impairment, if not of disease. It is true that many physicians recognize and acknowledge that some functional murmurs may be harmless, but when they attempt in their writings to deal with this problem, their words convey so confused an impression that it is evident that they have but a hazy conception of the manner in which a harmless or physiological murmur is to be distinguished from a murmur which may be an indication of, or associated with, heart failure.

The Sounds of the Heart

The first sound is produced by two factors, the contraction of the ventricular muscle and the sudden stretching of the mitral and tricuspid valves. Composed of these two elements, it is subject to many modifications, according to changes in the muscles or valves. Consequently, alteration in the character of the first sound is frequent, and satisfactory explanations for these variations are not forthcoming. Moreover, experience has shown us that little can be made out of these modified sounds alone, and while the modification should be noted, the real opinion of the heart's condition should be based on other evidences, which are never lacking. A certain number of modified first sounds have gained a place in the terminology of cardiac affections, and therefore need a brief reference.

Feebleness or absence of the first sound may indicate extreme exhaustion of the heart muscle, in the presence of other signs of heart exhaustion.

A "flapping" first sound is sometimes spoken of as indicative of a thin-walled ventricle, but we must be chary of trusting to such a sign.

A reduplication of the first sound may be due to a slight difference in the time of contraction of the two ventricles, or at least to a minute difference in the times of the closure of the mitral and tricuspid valves. Recently it has been found that a reduplicated first sound may indicate damage to the branch of the auriculo-ventricular bundle leading to the right ventricle, thus giving a lack of synchronism in the time of the contraction of the two ventricles.

The second sound is valvular in its production. An accentuation of the aortic sound is present when the aortic pressure is raised, and the pulmonary second sound may be found slightly accentuated when there is engorgement of the lungs; its cause is likewise due to increased pressure in the pulmonary artery.

Reduplication of the second sound is loudest usually at the mitral area. It is not clear how it is produced, but it is so often present in mitral stenosis that its detection should always arouse the suspicion of stenosis of the mitral valve in the absence of more reliable evidence.

A curious modification of the sounds of the heart is found when there appears a third sound, interpolated between the first and second sounds. The triple heart sound or gallop rhythm has been the cause of a good deal of controversy. There appear to be different conditions producing it; one of those is the reduplication of the first sound as already mentioned, due to a lesion of the right branch of the auriculo-ventricular bundle. Some have looked upon it as a grave sign, and no doubt it occurs towards the end of heart failure in such conditions as kidney disease; but I have found it in individuals who were free from any cardiac lesion, and who have lived for many years with no evidence of heart failure. Muffled sounds seem to be of little significance; sometimes they change into murmurs.

Physiological and Functional Murmurs

There are some murmurs whose nature is so obscure that they are still the subject of discussion. Some can with fair certainty be referred to definite orifices of the heart. Organic murmurs are due to lesions affecting the valves, and these can often be identified by certain peculiarities of the murmurs. There are, however, murmurs which arise when there is no lesion of the valves; these are spoken of as functional murmurs, but many are really physiological in the sense that the hearts exhibiting them show no signs of failure during life. The functional murmur usually occurs during ventricular systole, and may be heard in various regions of the heart. When heard loudest at the apex, it is assumed to be mitral in origin; when loudest over the middle of the sternum it is supposed to be tricuspid in origin. These murmurs are not infrequently heard loudest towards the base of the heart, and it is difficult to determine in which particular region, tricuspid, aortic or pulmonary, they are heard loudest, and it is sometimes suggested they are "cardio-pulmonary" in origin. It is not possible in all cases to distinguish them from organic murmurs. Much study has been devoted towards finding out if the mitral functional murmur could not be distinguished from the organic murmur because of its character and the regions into which it is propagated. While many organic murmurs do show very characteristic features, others resemble functional murmurs so closely that it is not always possible to speak with certainty.

Functional murmurs are usually assumed to be due to dilatation of the heart, rendering the orifices so wide that the valves fail to close them. This is not entirely correct, for while it is true that we may find a murmur with dilatation of the heart, we may often find great dilatation and no murmur. Further, we find murmurs come and go when there is no perceptible change in the size of the heart, the murmurs appearing only when the heart is excited or when the individual stands, and disappearing when the heart quiets or the individual is at rest. Again, murmurs which we find when the heart is acting quietly with the body at rest, may disappear on exertion or excitement.

From this it can be inferred that there is some special mechanism, apart from that involved in the dilatation of auricle and ventricle as a whole, and this obscure mechanism varies under circumstances which we are still unable to appreciate. The importance of this matter arises chiefly in connection with the heart of the young, where it is probable that the heart has a peculiar power of adapting itself, which is gradually lost in adult life. It must be remembered also that free regurgitation can take place at the mitral and tricuspid orifices without murmurs. We frequently get evidence of marked tricuspid regurgitation in the veins of the neck and in the liver, with no tricuspid murmur.

The chief importance attached to these systolic murmurs is that they are supposed to be due to blood escaping back from the contracting chamber. This regurgitation has been assumed to be the chief factor in producing heart failure, and from this conception has arisen the back pressure theory of heart failure. There are no accurate data to show the quantity of regurgitant blood necessary to produce a murmur, and we are forced to estimate the amount by indirect methods. I have been able to keep under observation, for twenty or thirty years, individuals with loud, rasping systolic mitral murmurs, and who gave a history of rheumatic fever, so that I could safely conclude that the murmurs were due to some damage of the mitral valves. These patients never suffered from heart failure; and I venture the conclusion that, in them, the leak was small and the damage slight, so that one may say, within certain limits, that in regard to mitral murmurs the narrower the orifice the louder the murmur. Where there are functional murmurs, the leak, if there be a leak, is so slight that it never embarrasses the auricles in their work, apart from cases where there exists grave damage in the heart muscle. The small quantity of blood thrown back does not alter appreciably the size of the auricles, for we often find murmurs in hearts of the normal size.

The Differentiation of Functional and Organic Murmurs

It is not always easy to distinguish between functional and organic murmurs. As a rule functional murmurs are systolic in time and are heard loudest over different parts of the heart. They are usually soft and blowing, but these characteristics do not distinguish them from some organic murmurs. Much has been written to determine the different features; but while organic murmurs often may be characteristic, both in their character and propagation they resemble functional murmurs so closely that it is not possible in all cases to differentiate them. A very rough murmur, especially if accompanied by a purring tremor or a musical note, is indicative of a valve lesion. In the early stages, however, of an endocarditis the murmur is usually soft and blowing, resembling a functional murmur.

To distinguish between these two murmurs the whole circumstances of the case must be considered. In the first place, it is necessary to bear in mind that a murmur may be a normal event. When we find a systolic murmur occurring in an individual in robust health with no other cardiac sign, as a thrill or increased size of the heart, we may consider it as indicative neither of impairment nor disease. On the other hand, when we find a murmur occurring in debilitated persons, search should be made for conditions which account for the debility, as anemia, imperfect nourishment, insufficient rest, or disease of other organs. It is of importance to differentiate these murmurs in febrile cases, or after the subsidence of an acute febrile attack, as after rheumatic fever. The question then arises whether the heart has been affected by the disease process. Here it is necessary to bear in mind that the raised temperature alone may produce changes in the heart's action, such as increase in size and murmurs, so that during the febrile stage of such acute illness judgment should be suspended until more definite signs of an organic lesion are forthcoming. The persistence of a murmur after a febrile attack, or its appearance, should be considered along with the other evidences. Thus, after the subsidence of the fever, if the rate becomes slow and the youthful type of irregularity is developed, it may be assumed that the heart has escaped infection and that the murmur is functional. If, on the other hand, the rate is persistently increased, then the fear is that the heart has become infected, and that active changes are going on.

The Significance of Systolic Murmurs

Seeing that individuals with systolic murmurs may be in perfect health, leading strenuous lives, and never show any sign of heart failure, we may conclude that murmurs may be a physiological and normal sign, and indicate no impairment of the heart's efficiency, nor foreshadow the oncoming of heart failure.

I wish to insist upon this fact, for the possibility that a healthy heart may present a murmur is so opposed to the views of a great many of the profession, teachers and practitioners, that much harm is done to people who have to be examined for life insurance or for entrance to the services. I base my views on the fact that I have watched numbers of healthy young people, who exhibited this murmur, grow up into manhood and womanhood, and lead healthy and vigorous lives, and never show the slightest sign of heart failure. Moreover, if we consider how little we know of the causation of murmurs, it will be realized how little justification we have for treating them as abnormalities. Even if they were due to regurgitation, it is quite conceivable that the regurgitation might be consonant with a good functioning heart. I have already pointed out that the fear of regurgitation has attained the dimensions of a bogy in the medical mind; further, I have already pointed out that, even with organic disease, the amount of regurgitation required to produce a murmur is very slight. Functional murmurs may be present in debilitated individuals, and in these cases the murmur is not necessarily an indication of disease or impairment of the heart, nor is the valve incompetency which its presence indicates the cause of the debility. Manifestly, the murmur is then but one of the many symptoms which the individual may exhibit, and the diagnosis of such cases will necessitate a search for other evidences which may throw light on the cause of the debility. A systolic murmur may be present in cases of grave heart failure, but in such cases the murmur is but an associated symptom; for the valvular incompetence is not the cause of the heart failure, but is merely one of the changes which have arisen in consequence of impaired functional efficiency of the heart muscle.

The Significance of Organic Murmurs

Organic murmurs have a varied significance, and it is necessary to grasp the idea that, though murmurs are associated with heart failure, the valve lesions which they indicate are in the most instances not the cause of it.

It is also well to bear in mind that individuals with murmurs due to damaged valves caused by some infective disease, such as rheumatic fever, may lead vigorous lives and be engaged in strenuous occupations, and never show any sign of heart failure. From this we can conclude that valve lesions in themselves may not necessarily be of serious significance. As, however, murmurs are often associated with heart failure, the presence of organic murmurs should be considered from the following standpoints: (1) as an indication that the heart has been invaded by a disease process; (2) whether the damage done by the disease process is stationary or slowly progressive; (3) whether the disease process has affected and impaired the heart muscle at the same time; and (4) whether the damage of the valve is such that it obstructs the work of the heart, so as to embarrass the muscle and impair its efficiency. In acute illnesses, it will not be possible to answer these questions, for there the immediate question concerns the acute affections. In chronic cases, that is to say what is called chronic valvular disease, it is absolutely necessary that these questions should be considered and answered, if a rational conclusion is to be obtained. The manner of obtaining the knowledge necessary to answer these questions will be dealt with in the description of the different valve lesions.

The estimation of the significance of murmurs, like all other signs, should not be based on the murmur itself, but on the functional efficiency of the heart, and on the presence or abscence of other signs of cardiac affections (size, rate, and rhythm.) If we find in a heart of normal size and rhythm (or with the "youthful type" of irregularity) a systolic murmur without any sign of cardiac inefficiency, we may conclude that the heart is perfectly normal. If there be evidence of weakness, or other signs of abnormal conditions present, then the opinion should be based on these other signs, and not on the murmur.

Diseases of the Valves

Tricuspid Insufficiency

John Hunter drew attention to the fact that in the normal heart the size of the tricuspid valves was not sufficient to close the tricuspid orifice. Since then other anatomists have also described this normal incompetency of the tricuspid valves, and physiologists and others have found it present also in animals. In the routine examination of patients in health, as well as when debilitated, a systolic murmur, presumably tricuspid in origin, is not infrequent. The murmur is heard loudest over the sternum at the level of the third and fourth costal cartilages, and is not propagated beyond the apex nor into the carotids.

I refer to this normal incompetence of the tricuspid valve because a false idea of the significance of tricuspid regurgitation has crept into medical literature which has led to a misunderstanding of the nature of heart failure and of the significance of the pulsation of the jugular vein and of the liver. This has arisen through the back pressure conception of the heart failure, in which it was assumed that heart failure started by the giving way of the mitral valve which embarrassed the left auricle and the circulation in the lungs, followed by embarrassment of the right ventricle, and giving way of the tricuspid valves, so that tricuspid regurgitation was supposed to be the last stage of this disastrous process and such signs as dropsy, enlargement and pulsation of the liver, congestion of the spleen and kidneys, were supposed to be the outcome of tricuspid regurgitation. No doubt tricuspid regurgitation is present in such cases, but it has about as much to do with the causation of these signs as the spoon has to do with the nutrition of the body. Had physicians, who have adopted the back pressure theory of heart failure, but watched their patients as the phenomena arose, they would have observed that the result of heart failure frequently coincided with the symptoms of the condition now called auricular fibrillation, and the characteristic pulsation in the jugular and liver was an evidence of the appearance of the abnormal rhythm (Fig. 6) as shown by the disappearance of the waves due to the auricle, and by the associated disappearance of the presystolic element of the murmurs in mitral stenosis. These changes are shown semi-diagrammatically in Figs. 8 and 9. Although it is many years since I drew attention to these facts and pointed out though back pressure is no doubt one factor in heart failure, it is not usually a matter of much importance so far as mitral and tricuspid regurgitation is concerned, yet in recent literature I find the old descriptions given and even my own tracings of the jugular (Fig. 6) used as proving the presence of tricuspid

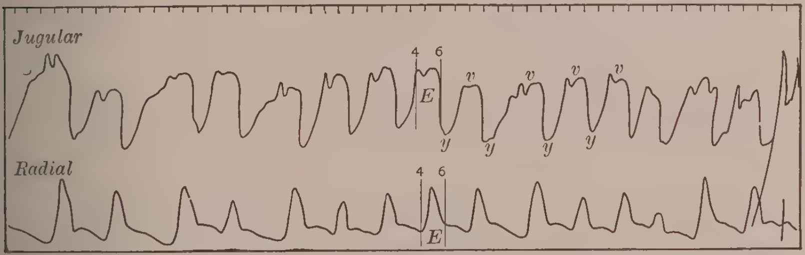

Fig. 6.—Simultaneous tracings of the jugular and radial pulses. The jugular pulse is of the ventricular type, there being no wave due to the auricle preceding the ventricular systole. The wave *v* occurs solely during the ventricular systole–Space E. While tricuspid regurgitation is present, the peculiar significance of this form of jugular pulse is that it indicates the presence of auricular fibrillation, shown also by the characteristic irregularity.

regurgitation, while the real significance as demonstrating the presence of auricular fibrillation has been lost sight of.

When the auricle is active with tricuspid regurgitation the jugular pulse is not of the ventricular type, but is of the auricular type, as is shown in Fig. 7. It is only when the auricle ceases to be active that the ventricular jugular pulse appears (Fig. 6.) It will thus be seen that tricuspid regurgitation is of little practical importance when a systolic murmur is perceived, and the extreme signs of heart failure are not brought about by the tricuspid regurgitation but by the failure of the heart muscle to send the blood around the circulatory system with sufficient force. It must not, however, be assumed that tricuspid regurgitation is not present in the absence of a murmur, for we will often find a jugular and liver pulse of the ventricular form without a murmur, and at the post-mortem a greatly dilated tricuspid orifice may be detected. A weak muscular wall and a wide orifice may give rise to no murmur.

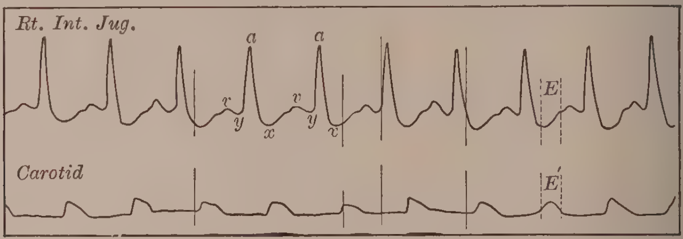

FIG. 7.—Simultaneous tracings of jugular and carotid pulses. The jugular pulse is of the auricular type, there being a large wave, *a*, due to the auricle. (Compare with Fig. 6.) In this patient the tricuspid valves were partially destroyed and the orifice was incompetent, so that there was free tricuspid regurgitation, showing, therefore, that tricuspid regurgitation does not of itself produce the ventricular type of jugular pulse.

Organic lesions of the tricuspid valves are rare, and are nearly always associated with similar lesions in the mitral and aortic valves. The heart failure associated with these lesions is never due to the tricuspid lesion alone.

TRICUSPID STENOSIS

In the majority of cases, tricuspid stenosis is not recognized during life, as the symptoms produced are not always distinctive. It is only rarely that a presystolic tricuspid murmur is heard; I have only heard it in three cases, in which it was present in a very limited area over the middle of the sternum. There is usually present also a mitral presystolic murmur at the apex, but as each murmur is confined to limited regions, I have had no difficulty in distinguishing them. In one case, the auricle had become so greatly hypertrophied that it sent back a large wave into the jugular and with such force that it caused the valves in the jugular and subclavian veins to close with a snap, which I could hear over these veins as a clear, sharp sound preceding the first sound of the heart.

As a result of the stenosis of the tricuspid orifice, the right auricle hypertrophies, and on this account sends a wave back with such force that it distends the liver, and therefore I look upon pulsation of the liver with a marked wave due to the auricle as suggesting the presence of tricuspid stenosis.

Mitral Regurgitation

Mitral regurgitation may be the result of a damaged valve, or of dilatation of the orifice from the giving way of the muscles supporting the valve. The murmur of mitral regurgitation is systolic in time, heard loudest at the apex. It may be soft and blowing, of little intensity, and heard over a very limited area, or propagated into the axilla; or it may be rough and loud, and heard over the whole heart and round to the back of the chest. It is not always possible to tell whether it is due to dilatation of the orifice or to damage of the valves. The rough, loud murmur with an accompanying thrill is always a sign of damaged valves.

When the muscle in unimpaired, little or no bad effect follows incompetence of the mitral valves. Even where the regurgitation is due to "functional" dilatation of the orifice, the contractile power of the muscle may maintain a good and efficient circulation and the patients enjoy perfect health with an efficient circulation. The really serious trouble in connection with mitral regurgitation arises when the muscle is impaired and the regurgitation may then add to its embarrassment. Few symptoms of heart failure may be produced until the muscle gives way, which is manifested by the signs of heart failure. Dilatation is generally looked upon as the result of mitral regurgitation, the back pressure ultimately producing yielding of the walls of the right heart. This is not quite correct, for long before there is any back pressure we may find evidence of a dilated right heart. If we examine carefully the condition of the heart, when the valves have been damaged by rheumatic endocarditis, during one of the slight attacks of heart failure which are likely to occur after overexertion, we may find the heart slightly dilated, the right ventricle being in front so that the left ventricle is pushed to the left behind the lung; the apex beat is then due to the right ventricle, shown by an indrawing during systole. After a few days' rest and treatment, the right heart may retreat and the apex beat is then due to the left ventricle, the apex presenting the normal characters—an outthrust during systole. In such cases there is no evidence whatever of pulmonary engorgement and back pressure. In fact, where there is heart failure Graham Steele says, "the change in the valves is altogether inadequate to explain the evidently free regurgitation that occurred during life, and the disastrous dilatation of the heart. The muscle-failure factor, it may be presumed, was the essential one."

The damage to the valves is most commonly the result of rheumatic endocarditis, and, as we have seen, the process is rarely limited to the endocardium, but invades the myocardium. Septic endocarditis may also damage the valves. In all cases of mitral stenosis, there is mitral regurgitation, but the amount of the regurgitation is never so marked as to be the serious factor in the case.

Regurgitation occurs through the mitral orifice with the valves uninjured in the later stages of many affections, such as conditions that produce exhaustion of the heart muscle, but more particularly in renal disease and cardiosclerosis. Here the condition is brought about by the failure of the muscle to support the orifice, and this may be one sign of a final and fatal exhaustion of the heart muscle.

It will thus be seen that the symptoms produced by mitral incompetence are only of gravity when there is also muscle failure, and this is dealt with in sufficient detail under affections of the myocardium.

Mitral Stenosis

This is, perhaps, the most common of valvular defects with which heart failure is associated. It arises generally in consequence of rheumatic endocarditis, though it may be found in people with no rheumatic history, and a previous history of erysipelas or some other febrile complaint may give a possible clue to its origin.

The condition is never recognized during the acute process which induces it, for the reason that stenosis does not occur till the cicatrizing process following the inflammation narrows the orifice, and on account of its origin in scar-formation, it is often a progressive lesion. Once the stenosis is present it may remain moderate in amount, and offer so little embarrassment to the heart that patients may reach extreme old age with no heart failure. As a rule, however, the cicatrizing process goes on with varying rapidity until in some cases the mitral orifice is reduced to a mere slit, and the valves resemble a thickened calcareous diaphragm. It is important to bear in mind the progressive nature of the lesion, for it accounts for the varying changes in the symptoms. It should also be borne in mind that a similar cicatrizing process may be going on in the muscle, causing contraction of the chordae tendineae, impairing at other places the functional activity of the heart muscle, and affecting the auriculo-ventricular bundle, depressing the conductivity or producing the conditions which lead to auricular fibrillation, thereby profoundly affecting the efficiency of the heart and modifying the nature of its rhythm.

From this it can readily be understood that the manner in which heart failure is brought about is somewhat complicated. In some, embarrassment may not ensue until the narrowing of the orifice has become extreme. In others there may be a fatal issue while the narrowing is yet moderate. In the latter cases, the muscle wall inevitably will be found to have been damaged.

The murmurs present in mitral stenosis, the presystolic murmur or the auricular systolic, are due to the contraction of the left auricle forcing blood through the narrowed mitral orifice. With the advancing cicatrization, the murmurs of mitral stenosis alter and present pecularities that hitherto have not been sufficiently appreciated. In the very early stages, some years before the appearance of a murmur, I have detected a slight presystolic thrill. The first murmur to appear precedes, or runs up to, and seems to terminate in the first sound, and is audible over a small area around the apex. At first it may not be always present. This murmur may vary in duration, being usually short and abrupt, but it sometimes begins earlier and is somewhat prolonged. It is of a crescendo character, rising in pitch till it ends in the first sound.

With advancing stenosis of the orifice, another murmur makes its appearance, namely, one occurring immediately after the second sound, heard only in the immediate neighborhood of the apex beat. At first it is very faint, and not very constant, but it usually increases in duration until the whole diastolic period may be filled up by it. This diastolic mitral murmur diminishes in intensity from the beginning, differing thus in its diminuendo character from that of the presystolic. Frequently we can detect a continuous murmur during the diastole of the heart, beginning loudly, falling away, then increasing in intensity. The first or diminuendo portion of such a murmur is the diastolic mitral murmur, while the terminal crescendo portion is the presytolic. The cause of the diminuendo diastolic mitral murmur is the flow of the blood that has been accumulated in the auricle during the ventricular systole, through the narrowed mitral orifice; this begins as soon as the mitral valves open, that is, when the pressure in the ventricle falls below that in the auricle. The development of these murmurs is shown in Fig. 8.

The next change in the character of these murmurs is the sudden disappearance of the presystolic crescendo murmur, while the diastolic murmur persists. Usually this change occurs with the onset of grave symptoms of heart failure, the heart's action becoming rapid and irregular. At other times, the change takes place with no serious symptom, but the heart invariably becomes irregular. This is due to the fact that the rhythm of the heart starts no longer with an effective auricular systole, but the auricle ceases to contract as a whole, being in the condition of fibrillation (Fig. 9).

When the heart's action is slow, there is no difficulty in recognizing the diastolic murmur, and the absence of the presystolic. The diastolic murmur is sometimes of great length, starting immediately after the second sound, and when the heart's action is rapid it may fill up the whole diastolic pause, and it might hastily be assumed that the murmur was presystolic. But if the heart be carefully auscultated it will be found that it is not crescendo in character; when a longer pause occurs, it will be found that the murmur stops short before the first sound, so that there is a silence between the end of the murmur and the first sound (see Fig. 9). In these cases, the jugular and liver pulses are invariably of the ventricular form. From the progressive nature of the lesions in the valve and in the heart muscle, it will be realized that the symptoms are not constant. The patient comes first into consideration mostly in early or middle adult life. The complaints, then, are shortness of breath, a sense of suffocation, and palpitation on exertion. In some the face is ruddy, with a hue a shade darker than is compatible with the ruddy countenance of robust health; in others there is pallor. At this stage there is little or no increase in the size of the heart and no dropsy. A presystolic murmur can usually be detected. The patient's complaints may be the only evidence we have of the heart failure, and these point to an exhaustion of the reserve force. After a period of

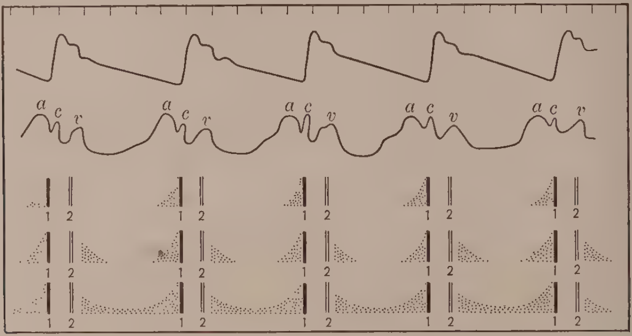

FIG. 8.—Tracings of the radial and jugular pulse with diagrammatic representation of the changes in the murmurs of mitral stenosis. The down strokes 1 and 2 represent the first and second sounds of the heart. The first indication of stenosis is the appearance of the murmur before the first sound, and on reference to the jugular tracing this murmur will be found to coincide in time with the wave, *a*, due to the systole of the auricle. With an increase in the stenosis, a short diastolic murmur appears, immediately after the second sound, and this is represented in the middle diagram. A further increase in the stenosis, shown in the lowest diagram, leads to prolongation of the diastolic murmur, which in combination with the presystolic murmur fills up the whole interval between the second and first sounds. (For the next change see Fig. 9.)

rest, this exhaustion may disappear, and the patient may go on for years with little further trouble. After a time, however, some again break down and the symptoms complained of may be of the same nature. Frequently, however, a change is found in the character of the murmurs, a diastolic murmur usually being perceived, and there is sometimes a longer duration of the thrill, these signs implying an increased narrowing of the orifice. On the other hand, in those in whom no further narrowing takes place, the murmur does not change, and the patient may go on for many years, and, if a female, she may bear children with no breakdown. In these cases we can infer that there is no progressive muscular or valvular sclerosis. With the increased narrowing of the orifice, as indicated by the appearance of the diastolic mitral murmur, the heart becomes much embarrassed, the symptoms become much more distressing, and finally dilatation of the heart may set in. But even without the progressive narrowing, dilatation may appear early, and then it may be inferred with certainty that the rheumatic process has permanently injured the heart muscle. It is to be noted that frequently the left ventricle also dilates, showing that there is some vital factor concerned in dilatation.

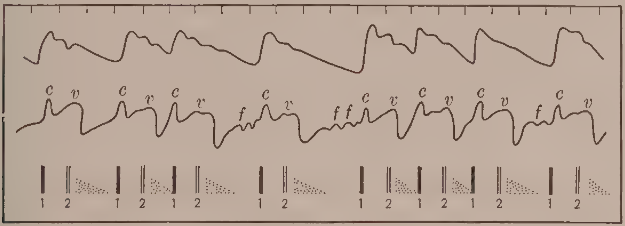

FIG. 9.—After the changes described in Fig. 8 the next change is a sudden alteration of the rhythm of the heart. In Fig. 8 the heart is quite regular; in Fig. 9 it is irregular. The wave, *a*, which is a marked feature in the jugular tracing of Fig. 8 is absent in Fig. 9. The presystolic portion of the murmur is also absent in Fig. 9, this feature being best appreciated during the longer pauses. The disappearance of these evidences of auricular activity and the irregular action of the heart indicate the onset of auricular fibrillation. The waves *ff* are due to the fibrillating auricle.

The rhythm of the heart may become continuously irregular with the onset of auricular fibrillation and further embarrassment arises. If there be no change in the size of the heart with auricular fibrillation, and no great acceleration of rate, the heart failure may be very slight in degree; but if the heart dilates, especially if the rate is accelerated, then all the extreme symptoms of heart failure follow (dropsy, enlargement of the liver, etc.).

In the vast majority of cases, the heart recovers from its first breakdown, and usually from many subsequent attacks. Indeed, after one attack, I have known patients go on for twenty years and more, with no further trouble beyond a slight limitation of the field of response to effort.

After repeated attacks, the patient's life becomes one of great limitation. The future depends often on the rapidity of the advance of the sclerotic process of the valves and the heart muscle. If the rate of advance be slow, and the heart muscle capable of responding to treatment, the patient may go on for many years with a crippled existence. Sometimes at the post-mortem examination we find in the young, about twenty years of age, the orifice narrowed to a mere slit. In others we find the mitral orifice not much contracted, but the heart wall greatly dilated and evidence of fibrosis of the muscle. Hence it will be seen that the progress of these cases is largely dependent on the rate of change in the muscle as well as in the valve. The final issue is usually by great extension of the dropsy and exhaustion.

The damage done by the rheumatic fever may effect other structures than the valves, and as a result we get some curious effects upon the rate and rhythm of the heart. The most common is an invasion of the auriculo-ventricular bundle giving rise to a slight degree of heart block similar to that shown in Fig. 1. This may appear during the causative attack of rheumatic fever, or it may only show itself in after years. Usually there is no sign of its presence unless a graphic record of the jugular pulse or an electrocardiogram is taken. Occasionally it can be recognized by the dropping out of a ventricular beat, as in Fig. 1, when the stimulus from the auricle fails to pass to the ventricle. This is apt to occur during the administration of digitalis.

An interesting evidence of heart block is found in the mid-diastolic murmur. When mitral stenosis is present and there is a mild degree of heart block, there is a delay after the murmur due to the auricular systole before the first sound occurs. If a graphic record of the jugular pulse be taken there will be found a wave due to the auricular systole, and this exactly synchronizes with the time of the murmur, so that a mid-diastolic murmur is an evidence not only of mitral stenosis but of partial heart block, evidence, that is, of a damaged mitral valve and a damaged heart muscle.

In advanced cases when there has been myocardial damage, a curious variety of phenomena may appear, especially under the influence of digitalis. Thus attacks of paroxysmal tachycardia, due to auricular flutter and auricular fibrillation, may occur spontaneously. I have seen in a few cases the latter condition arising from the administration of digitalis. In one case, with a mid-diastolic murmur, digitalis had a very peculiar effect, causing a standstill of the whole heart, and when the heart started the ventricle began before the auricle (Fig. 10).

At various stages patients may be seized with great bleeding from the lungs. Here, doubtless, the cause is engorgement of the pulmonary circulation and rupture of a blood vessel. As a rule, this is a grave sign, the patient dying sometimes shortly after an attack, although in auricular fibrillation the patient may make a good recovery, especially if the heart is susceptible to digitalis. In rare cases the curious and usually fatal condition, suffocative edema of the lungs, may unexpectedly occur.

Vegetations may grow on the mitral valves with no certain sign of their presence until a small portion is detached and, impacted in some vessel, gives rise to a hemiplegic attack, or an attack of aphasia. Usually recovery takes place speedily and may be permanent, but cases have been recorded in which the aphasia or hemiplegia has remained complete for many years. Clotting may occur in the auricular appendage during auricular fibrillation and be a source of embolic infarct.

Attacks of angina pectoris, although very rare, may occur in mitral stenosis. In the few cases I have observed, they were all secondary to some excessive exertion, and the patients had only one or two attacks, remaining perfectly free from them for years afterwards.

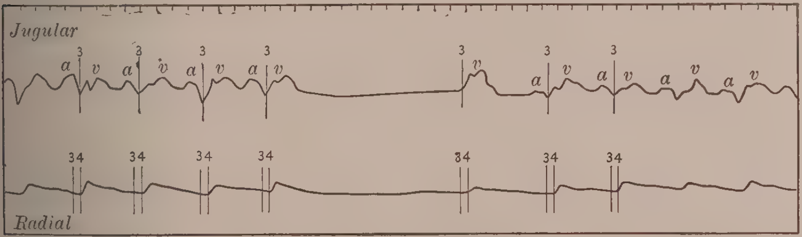

FIG. 10.—Simultaneous tracings of the pulsation in the jugular at the same time as the radial, showing the temporary arrest of the whole heart from digitalis. The first beat after the long pause is an escaped ventricular beat, there being no auricular beat preceding it. The waves *a* are due to the auricle, and the waves *v* are due to the ventricle.

AORTIC STENOSIS

Aortic stenosis is often associated with aortic regurgitation, and the symptoms of the latter usually dominate the situation. When there is little or no regurgitation, the murmur of aortic stenosis may only be detected in the routine examination of the patient.

Aortic stenosis which embarrasses the left ventricle is by itself a rare condition; I have only seen it in a few elderly people in whom there was a syphilitic history. A systolic murmur at the base of the heart should never be taken as indication of aortic stenosis without other characteristic signs. Such a murmur is not uncommon in the healthy young, and it may appear in middle age. I have followed cases showing this murmur for twenty to thirty years, and in none have there been any serious consequences caused by the condition giving rise to the murmur. How it is produced I do not know.

The sign characteristic of aortic stenosis is a murmur systolic in time, heard loudest over the second right costal cartilage, propagated into the carotids, and accompanied by a thrill perceptible over the upper part of the chest wall. The heart's rate is often slow, between fifty and sixty beats per minute. The radial pulse is sometimes very characteristic. It impinges against the finger in a slow, leisurely fashion, and a sphygmographic tracing may show a slanting up-stroke with a slight interruption near the summit (anacrotic pulse) or even a double wave at the top (pulsus bisferiens).

Besides these signs, there is little that is characteristic in aortic stenosis. There may be symptoms of angina pectoris, but these are due to associated changes in the heart muscle, and other evidences of heart failure can be referred to the same cause.

Aortic Regurgitation

The aortic valves, being contracted, are no longer able to support efficiently the column of arterial blood during the diastole, but permit a backward flow into the heart, and as a result, we find certain alterations in the character of the second sound and of the arterial pulse. The closure of the valves no longer gives to the second sound the characteristic snap, but the sound ends in a murmur sometimes long drawn out, sometimes so brief as to be scarcely perceptible, as if the second sound terminated not abruptly but with a faint sigh. The diastolic murmur is usually propagated down the sternum, but sometimes it is heard loudest at the apex. It has been suggested that this variation in the propagation of the murmur depends on the direction given to the backward flow by the position of the retracted cusp. This seems plausible, but I have not been able to verify it, and the explanation is ignored in recent textbooks.

The regurgitant murmur is usually associated with the murmur of aortic stenosis, and we get the characteristic double aortic murmur (bellows murmur). There is frequently dilatation of the smaller arteries, and this, combined with the effect of the regurgitation on the arterial pulse, causes the artery to become emptier than usual towards the end of diastole. This means a fall of pressure, and in order to maintain a normal mean pressure, the heart increases the force of its contractions, raising the pressure during systole, so that there is a great increase in the systolic pressure and a great fall during diastole, thus giving rise to the characteristic collapsing pulse (Corrigan's pulse, the water-hammer pulse). The collapsing character of the radial pulse may be intensified by raising the arm above the head. At times the arterial pulse is conveyed through the capillaries into the veins and is visible on the back of the hand. If the forehead be rubbed so as to produce redness, the flush is seen to wax and wane with each beat of the heart (capillary pulsation) and these same phenomena appear in the finger nails.

The double aortic murmur may be present without any history of a heart affection. In many cases, there may be little or no dilatation, and the individual may be able to indulge in games and in occupations requiring considerable exertion with no discomfort. In such cases, it may safely be assumed that the damage to the valves has been slight, and that the heart muscle has escaped serious injury.

In other cases, the heart is greatly enlarged, and the apex beat is diffuse and forcible. The systole and diastole of the heart may cause movements of the liver that simulate pulsation of that organ, but analysis of its graphic records show it to be merely the dragging up and pushing down of the liver by the changes in the size of the heart. Even under these circumstances, the individual may for years pursue an active life, but he is always liable to attacks of heart failure. The condition is often associated with diseases of the mitral valves, and this is one of the factors participating in the production of the heart failure that finally terminates these cases.

The most frequent sufferers from heart failure due to aortic valvular disease are in middle age. In them the sclerotic process has been gradually advancing, and the early symptoms of exhausted reserve force have been neglected until symptoms of distress command attention. There may have been a history of rheumatism, of excessive drinking, or hard bodily exertion, of syphilis, but on the other hand, no definite causal condition may be discovered. The facial aspect is frequently of a pale gray (earthy countenance), though in others in whom there are other complications it may be full-blooded and ruddy. The complaints are varied. Shortness of breath on exertion, violent throbbing in the neck, attacks of pain over the chest on exertion, are amongst the most common symptoms of which the patient complains in the early stages of heart failure. For a varying period, under suitable treatment, a certain store of reserve force is gained, and he may go on for months or years, sometimes in fair comfort, but his existence is usually more or less crippled after the appearance of signs of functional inefficiency.

A feature strikingly characteristic of aortic regurgitation is the susceptibility to nerve stimulation. The heart and blood vessels are readily stimulated, the former to rapid action, the latter to variations in the caliber of the vessels. The recognition of this peculiarity is of importance; for I have repeatedly seen individuals in whom the heart became rapid in action, and with consequent exhaustion, when they were first informed they had an affection of the heart. Moreover, these cases are very susceptible to a mental stimulus, which may increase the heart rate, and also raise the blood pressure and induce attacks of angina pectoris. The difference of the blood pressure in the arteries of the arm and leg has been commented on and also the susceptibility to attacks of pain.

The end of these patients is very varied. Many aortic cases suffer from extreme exhaustion, and may show no objective signs of heart failure, such as dropsy. Where there is dilatation and dropsy, it is generally because there is present some disease of the muscle wall, as shown by the presence of auricular fibrillation. Some of the most intractable cases of auricular fibrillation are those where there is also aortic regurgitation, so that I look upon the appearance of auricular fibrillation in aortic cases as a somewhat grave event, more so than when it occurs with mitral stenosis. Those who suffer from angina pectoris may die suddenly. I have seen a few cases die during a sudden attack of dyspnea of the greatest severity.

PROGNOSIS

In estimating the value of any abnormal sign, or in determining the condition of the heart, the most reliable guide is the manner in which the heart responds to exertion. This, again, is but an attempt to estimate the amount of reserve force. If the individual can with comfort make such exertion as we would expect at his time of life, then the abnormality may with certainty be assumed to be of little real significance.

If there be a complete breakdown, the decision should not be made until time has shown to what extent recovery takes place. The amount of recovery enables us to judge the condition of the muscle of the heart, for it is on its capability to renew its reserve force that the future of the patient depends. An axiom, applicable to a great many cases, is that patients usually recover from their first attack of heart failure, however extreme it may be. The reason for this is that the patient has persistently been giving a crippled heart more work to do than it was fit for, so that a period of rest is sufficient to restore a measure of strength to the exhausted muscle.

Even cases that never show a complete restoration of function, and in which attacks of extreme failure are frequent, may go on for many years, and the individuals lead sometimes fairly useful lives, though in time the progressive changes become so great, or the muscle so exhausted, that the possibility of even temporary recovery is precluded.

In individuals in whom there is a distinct limitation of the field of cardiac response, a close scrutiny should be made into the cause. It should be borne in mind that if a heart is not properly exercised its field of response becomes more and more restricted. Thus a man who for a long time leads a sedentary life is often startled by the fact that he is rendered extremely breathless by undertaking some exertion that he was wont to make with ease a few years previously. But with moderate training, there is soon restored sufficient reserve force to enable him to perform his task without distress. Therefore, in all cases, even when there is an abnormal symptom, as a murmur or an irregularity, the nature of the exhaustion should be discovered. It must not be forgotten, also, that the supposed abnormality may have nothing to do with the symptoms of exhaustion. This is particularly the case in the young, in whom syncopal attacks are not infrequent. I have repeatedly seen grave alarm aroused because a boy or girl has fainted, and has had an irregular pulse when quiet in bed. This irregularity has been of the youthful type, and had no connection with the syncopal attacks and its presence in no sense added any gravity to the condition.

While the lines on which prognosis is based can be fairly well recognized in regard to the more common affections of the heart, we often meet with patients who show symptoms whose nature is too obscure for us to identify. A prognosis in these cases is often required and difficult to give. The plan I have adopted is to exclude the possibility of degenerated muscle by an examination of the condition of the heart muscle and particularly its efficiency as laid down under heart failure. We should always consider how far the subjective complaints may be nervous in origin. Having satisfied myself that the muscle is sound, I give a favorable prognosis, at the same time indicating the obscurity of the case. I do this because, as a matter of experience, I have found that these exceptional cases, particularly in young adults, always tend to recovery to a greater or less degree. This, unfortunately, is not the usual plan; for some signs are too often taken to be more serious the more obscure they are. In many cases, the physician must be prepared to back up his opinion by taking a certain amount of responsibility. For instance, I have on several occasions seen patients kept in bed and put through elaborate forms of treatment after an illness, as influenza, or an attack of angina pectoris. The patients have complained of obscure signs, to them alarming, and a certain amount of abnormality has been present, as a frequent pulse or extrasystoles. Having satisfied myself that there was no serious mischief, I have had no hesitation in making the patients get up and resume their ordinary life, even when the medical attendant has shrunk from the responsibility. I have never yet had cause to regret such a procedure, and it is better to run a little risk in a rare case than to have a patient drifting to invalidism, because of our ignorance and fear of responsibility.

Prognosis in Valvular Affections.—Let it always be remembered that sound and healthy hearts may show a murmur, and that it is necessary, therefore, to seek for other evidences on which to base a prognosis. The heart failure which may be present depends upon so many and so varied conditions, as the extent of the valvular lesion, its progressive nature depending on the cicatrizing process affecting the valves, the coincident changes in the muscle and in the auriculo-ventricular bundle, the conditions of life of the individual, that no rule applicable to all cases can be made. If, however, an attempt be made to appreciate the value of the symptoms present, on the lines I have laid down, an approach to a true prognosis may be made in each case. There is just one point I again wish to insist upon: let no murmur be the ground for forming an unfavorable prognosis. In this respect, the presence of a murmur has so oppressed the profession that a vast amount of positive harm is continually being done to patients by an imperfect understanding of the prognostic significance of this sign. The field of cardiac response is the only true and safe guide in these cases. If for the time being this is limited, judgment should be suspended until an opportunity has been obtained for ascertaining to what extent the heart muscle can regain a store of reserve force.

Treatment of Heart Disease

The highest aim of the medical profession is to prevent and cure disease. Unfortunately, this is rarely possible, and the chief occupation of the doctor is the relief of suffering and the attempt to modify the course of disease. As has been pointed out, diseases of the heart are already present in the vast majority of cases when the doctor sees the patient, so that the most he can do is to make the best of a damaged heart. Fortunately, in the majority of cases, if the doctor understands the source of danger and recognizes the signs which indicate danger, he can do a great deal for his patient. But this question of understanding the significance of signs is a matter of the greatest importance. The knowledge that death comes frequently through heart affections oppresses patients and doctor. The former being told his heart is affected becomes willing to submit to treatment and restrictions that hold out the hope of recovery. The doctor, having no clear idea of the significance of signs, employs too often all sorts of methods in the hope that he may, by good fortune, help his patient. In the past the absence of a clear idea of the source of danger led to the assumption that practically every abnormal sign, or what was taken for an abnormal sign, was a call for treatment. The statement that signs, such as murmurs or irregularities, were frequently of no serious significance, were indeed physiological manifestations indicative neither of disease nor impairment, is received today by many doctors as incredible. The fact that a great many people who show these signs are in perfect health but have been subjected to treatment and have afterwards led vigorous lives, has been taken as an evidence, not of the innocence of the symptoms, but of the efficiency of the treatment. For this reason there is now recommended for treatment of affections of the heart such a great number of methods, drugs, baths, exercises, that the utmost confusion surrounds a matter which can be rendered simple and easy of comprehension when the fundamental principles of therapy are understood.

To appreciate these principles, it is necessary to grasp wherein the danger lies. The danger in every case of heart affection is that the heart may fail to maintain an efficient circulation. I have already dealt fully with this matter and have shown that the maintenance of an efficient circulation depends on the integrity of the heart muscle. An inquiry into the signs which indicate heart failure showed that in the first instance the failing heart could be recognized by distress being provoked when the individual made some effort which he was wont to perform in comfort. The later stages of heart failure are exhibited by such signs as dropsy, enlarged liver, and orthopnea. That is to say, the signs of heart failure are shown by signs of a deficient circulation in other organs. This way of looking at the matter enables a classification of symptoms to be made which directs attention to their significance, inasmuch as it shows that the physical signs revealed by the examination of the heart itself, by the unaided senses or by mechanical devices, give no clue to the functional efficiency of the heart. The great importance of this classification will be seen when it is reflected that hitherto the discovery of a physical sign has been looked upon as an indication for treatment.

If, then, we bear in mind the view that heart failure begins by an exhaustion of reserve force, and is perceived only when exertion is made to the full amount of which the heart is capable, the first duty in treatment is to ascertain what circumstances have induced the heart failure. To this end an inquiry is made into the patient's condition to find out when he first became conscious of the limitations of his cardiac field to response. Then a searching examination is made into the circumstances preceding that period, as to the question of overwork, worry, sleeplessness, or infection. The inquiry next proceeds to the examination of the circulatory system, and any defect there must be considered from the point of view whether its presence embarrasses the heart in its work and whether the failure has been due to a gradual weakening of the heart from this cause. If the physician is careful to bear in mind that an abnormal sign is not necessarily an evidence in itself of disease, and that it is not the sign which has to be treated, but that the essential aim in the treatment of the heart failure is the restoration of the reserve force of the heart muscle, then he will have a sure guide in applying treatment to the diverse conditions, even when the symptoms are not fully understood. Before proceeding to treat the patient, we try to appreciate the value of his symptoms, subjective as well as objective. When we do find some abnormality on physical examination, its bearing upon the subjective sensations has to be considered on the lines already laid down, and all attendant circumstances that may have contributed to the heart failure must be taken into consideration. When we detect some actual cardiac defect and we do recognize that the heart failure is undoubtedly brought about by its presence, then, provided that we cannot remove the actual lesion, the object of treatment is to restore the exhausted muscle and place the patient in such a position that he can lead a life useful and free from discomfort, though hampered by an obstacle to the heart's full efficiency. We should keep steadily before our view the fact that the heart is impaired, and it is vain to attempt to restore the irremediable.

This suggestion may seem so self-evident as scarcely to need remarking, still less to be emphasized, but from practical observation I feel the necessity of insisting upon it, for patients with an incurable cardiac defect are continually being subjected to treatment whenever they consult a physician, and they may be found going to health resorts, year after year, under the impression that in some way or other the defect needs treatment. If the patient had an ankylosed joint or a wooden leg, it would be recognized that baths or drugs can do little for him, but the thickened edges of a mitral valve are supposed in some way to need constant treatment. The object of treatment should not be to try to remove what cannot be cured, but to make the best of what power the heart still possesses. In the nature of things, it may be that only a partial restoration of the heart can be looked for, and when we recognize that the fullest amount of recovery has been gained, judicious advice as to the future life of the patient may cause him to lead a life at a lower level, it is true, but still useful and interesting, and his years may be prolonged to the allotted span. Many individuals with a reserve force limited on account of inherent defects in the heart may never suffer from heart failure of any serious moment, and where the lesion is not a progressive one, they may suffer little inconvenience, provided that their limitations be appreciated by themselves and their medical advisers. It is in these cases that the advice of a wise physician is of great service. The knowledge of how much an individual may do, the permission to do as much as his reserve force will allow him without inducing exhaustion, can only be acquired by the full and careful consideration of all the individual symptoms. Much inconvenience may be caused to the patient by taking too grave a view of his cardiac defect, and so limiting him far too strictly, and hampering him in his life work, and oppressing him needlessly with the supposed gravity of his condition. On the other hand, the pursuits of a man whose heart is embarrassed by a grave defect may imperceptibly call too frequently on the full extent of the reserve force of the heart, and the period of rest being insufficient, exhaustion of the reserve force gradually proceeds, until heart failure of a more or less serious degree is induced. The work of man has attained a rough-and-ready standard in most trades and

CHAPTER XIV

DISEASES OF THE ARTERIES; ANEURYSM OF THE AORTA

By R. L. GIRDWOOD and SIR JAMES MACKENZIE

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Acute Arteritis

The external coat of the arteries is a modified part of the general connective tissue, and is continuous with it. Because of this intimate connection the arteries share in many of the diseases of the surrounding tissues. When a portion of the body is inflamed the walls of the arteries in that portion also become inflamed. Acute arteritis may start in the internal lining of the vessel, as when a septic embolus becomes impacted in a small branch. The arteries of the lower limbs, next to the aorta, are the most commonly attacked. According to some authorities the intima is exclusively attacked; according to others the vasa vasorum are often primarily attacked and the local condition is associated with a periarteritis. The symptoms are the symptoms of local inflammation, pain, redness and swelling; a feeble pulse will be felt if the vessel attacked be superficial. Gangrene may set in. Inflammation may be set up in the walls of the artery as a result of syphilis, rheumatic fever, influenza, pneumonia, smallpox and other fevers.

It is manifest that the prognosis and treatment of the various kinds of acute arteritis are dependent on the primary disease.

Chronic Diseases of the Arteries

Etiology.—Among the causes of chronic disease of the arteries may be mentioned senile decay, infections, especially syphilis, the circulation of poisons in the blood, as, for example, alcohol, lead, the toxins of gout, and the effects of Bright's disease and diabetes. It is also possible that poisons absorbed from a constipated bowel, as well as from a disordered digestion due to excessive feeding and drinking, may be the causes. Some of these conditions give rise to a raised blood pressure which may conceivably be both cause and effect of arterial structural change. Men who lead a strenuous life are subject to this condition, especially those whose work necessitates great and prolonged muscular effort, though the wear and tear of modern city life is also a factor apart from muscular strain.

Morbid Anatomy.—Much confusion surrounds the classification of chronic arterial diseases owing to the loose connotation of the terms. Regarding arteriosclerosis we propose atheroma and endarteritis deformans as synonymous, leaving proliferative or obliterative endarteritis to be described under syphilitic disease of the arteries, syphilis being with the other granulomatous diseases, the most common cause thereof (see section on Syphilis in chapter on The Circulation in Infectious and Toxic Processes by Ivy Mackenzie, Chap. X, Vol. II).

The essential lesion in arteriosclerosis is a thickening of the intima, especially of the subendothelial layer, which shows a great increase of connective tissue. Degenerative changes occur in the deepest part of this thickened area. The thickening may be localized in small patches or nodules or it may be diffuse and generally spread. The localized or nodular form is seen most commonly in the aorta and large vessels, especially near the orifices of branches and on and about the semi-lunar valves and the origins of the coronary arteries. The pulmonary arteries may be affected especially in cases of marked and prolonged mitral stenosis. These patches become a dull white or yellow color as fatty degeneration supervenes. Later lime salts are deposited, roughening the inner surface especially where the endothelium is lost. Here thrombosis is liable to occur. The middle and outer coats of the artery may show little or no change, but most commonly there is considerable overgrowth of fibrous tissue, especially opposite the patches of greatest thickening of the intima.

In the diffuse generalized form the arteries are dilated usually, and may be tortuous. Microscopically the subendothelial layer of the intima shows a great increase of connective tissue, often arranged in concentric layers, in which degenerative changes may be found. The media may show muscular hypertrophy in some cases, atrophy in others, or fibrous overgrowth and degenerative changes. The most commonly affected arteries in this diffuse form are those of the kidneys and brain, the changes being best seen in long-standing cases of Bright's disease. The lumen of the vessel may be almost occluded with the overgrowth of the intima. The capillaries are often thickened, especially those of the glomeruli of the kidneys. The sclerotic changes may even extend beyond the capillaries and affect the veins. The heart is enlarged. The muscle fibers may be much replaced by fibrous or fatty tissue. Where the coronary vessels are greatly involved, thrombosis may occur and areas of infarction and necrosis be seen. The kidneys show degenerative changes and fibrous overgrowth. The brain may show areas of softening and hemorrhages.

As already mentioned much confusion exists among authorities as to the nature of arterial disease, but an interesting and very suggestive classification of chronic arterial diseases, mainly from the clinical standpoint, is that given by Sir Thomas Clifford Allbutt in his "Diseases of the Arteries including Angina Pectoris." Emphasizing the points that arteriosclerosis and high blood pressure are not synonymous he distinguishes: (1) arteriosclerosis, the effect of persistently high blood pressures (hyperpiesia); (2) arteriosclerosis (toxic) the effect of certain poisons or toxins as of syphilis, typhoid fever, lead, diabetes, etc., in many of which the blood pressure is not necessarily or usually much increased, if at all, although in others, such as plumbism, it may be raised throughout; (3) arteriosclerosis (decrescent), the effect of senile involutionary changes, in which form again the arterial pressures, if increased, do not exceed the quasinormal increase which is general in later life, unless indeed hyperpiesia intervenes, as not infrequently it does.

Symptoms of Chronic Arterial Disease

The direct symptoms of chronic arterial disease are limited to the detection of changes in certain of the peripheral arteries which are palpable or whose movements are perceptible. In the healthy states only such superficial arteries as the temporal are occasionally perceptible. During excitement the movement of the other arteries, as the carotid, may be recognized. When the arterial walls become diseased, a number of superficial arteries with thickened and tortuous walls can be recognized, but the information of the effects of diseased arteries derived from this source is very small. It is the indirect symptoms that are of value, and they are chiefly exhibited by modification of the functions of the different organs, due to a diminution of their arterial blood supply.

Accompanying most of the chronic diseases of the arteries there is a disappearance of many capillaries. This is best seen in elderly people, healthy except that they show the signs which we associate with advancing years. In these, beyond a slight thickening of the wall of the radial artery, no sign of disease may be perceptible. But if one examines the skin, it is found frequently thin and attenuated, in some resembling tissue paper. If a cut be made through the skin and deeper tissues, as in an operation, the bleeding is no longer that free capillary oozing found in the young, but the oozing is scant and the bleeding is mainly from the spouting of a cut artery whose rigid walls remain open at the cut ends.

The symptoms of arterial disease of the arteries of the leg are shown in the first instance by the effects produced by the exercise of the muscles.

When elderly patients are asked what it is that prevents them walking rapidly on the level, some will reply that it is because of a sense of weight in their feet and pain in the neighborhood of their ankles. They also state that as soon as they stop the pain disappears. In extreme cases of arterial disease the sensation is one of cold in the feet, and as they persevere in walking, the cold passes into pain, and they have to stand still. After a brief period the feet become warm and the pain subsides. If the feet be examined after exertion, curious vasomotor changes can be seen in the skin, portions gradually paling and reddening. These experiences commonly precede gangrene of the toes and feet, and the symptoms are those usually described under the term "intermittent claudication," or "intermittent limp."

The arterial changes may be more advanced in other organs of the body, and symptoms peculiar to the organ are produced. When the arteries of the brain are affected we get symptoms of diminished blood supply, as giddiness, especially when standing up quickly from a lying position or on violent exertion, loss of memory, particularly for recent events, fatigue easily induced on applying the mind, as in reading a technical book. Sometimes irritability or temper or delusions of various sorts occur. These signs may be present only in a very slight degree before the presence of diseased arteries is revealed by a cerebral apoplexy.

The changes in the coronary arteries lead to a diminished supply of blood to the heart muscle, and their presence is revealed by a limitation of the power of the heart to respond to effort, so that an amount of exertion that had previously been performed with comfort now calls forth symptoms of distress, as breathlessness and pain. Indeed, angina pectoris is, in the most severe cases, due to the diminished supply of blood reaching the muscles of the heart because of the diseased coronary arteries, and the diminution of the capillaries. The degenerated arteries in the kidney result in the production of certain forms of Bright's disease, with the production of the symptoms characteristic of impaired renal function.

Prognosis in Chronic Arterial Disease

Though the arterial changes may be readily perceived, the prognosis is very difficult; indeed the prognosis can not be based upon the detection of any artery *per se.* It really depends on the manner in which the arteries permit a blood supply to the different organs, so that the factors on which a prognosis can be based are the character of the symptoms from such organs as the brain, the heart, the kidney and the feet, as they can be inferred from the description of symptoms.

When there is a possibility of the rupture of a diseased artery in the brain, no reliable information can be obtained from the condition of the palpable superficial arteries of the body, for it is found that a cerebral apoplexy may occur with no perceptible disease of the radials, while those with radials demonstrably diseased may not suffer from cerebral apoplexy. When, however, there is marked thickening of the radial with a high blood pressure, with or without albuminuria, cerebral apoplexy is one of the events likely to occur.

Treatment of Chronic Arterial Disease

The arterial disease is always far advanced before it is detected. Medical science has not yet advanced sufficiently far to be able to recognize this condition in its early stage, nor the circumstances that predispose or cause its onset, except in such a disease as syphilis. Nay more, we do not yet understand the steps which should be taken to acquire this knowledge. The lack of knowledge of the cause has not prevented the employment of many remedies, but it may be safely asserted that we know nothing that will restore a diseased artery to a healthy state, and it is doubtful if we have the means of checking the progress of chronic arterial disease.

Recognizing this and also recognizing the fact that the danger in arterial disease is its effect upon the organ, we are thus given an indication on what lines our knowledge at present may help the patient. Recognizing that such organs as the brain and the heart and the legs are accustomed to be exercised to the limit of their endurance, we must recognize the symptoms which indicate the exhaustion of these organs. As the persistent over-exertion of the organ leads to its deterioration, we must take the symptoms of exhaustion as our guide, and study the patient's mode of life and persuade him to lead a life well within the limits of his strength. Thus in the case of the heart, the first sign of exhaustion is a sensation of distress and pain or breathlessness. The onset of this sensation should be a signal for diminished effort, and if the patient will but recognize his sensations, he will have a safe guide as to the amount of effort he can undertake.

The same principles are applicable to the treatment of other organs when the exhaustion is induced by insufficient blood supply, as in the heart, brain and legs, and it may be, in the digestive system. We know too little of the effects of a diminished blood supply in other organs to be able to detect the signs of exhaustion which they produce.

FUNCTIONAL DISTURBANCES OF THE VASOMOTOR SYSTEM

There are a number of phenomena in which the arteries participate, especially the smaller vessels, because of their power of contraction and dilatation. The physiological reaction under certain circumstances may become so exaggerated as to constitute the chief picture in some diseases. Dilatation of the arteries is a characteristic feature in aortic regurgitation, in toxemias due to microbic infection and in the diseased function of certain glands, as the thyroid, which may cause a widespread dilatation of the arterioles.

The opposite effect, where there is a contraction of the arterioles and capillaries, produces a variety of distinctive phenomena. This normally occurs in exposure to cold, but this reaction may be so sensitive that cold may produce an extreme contraction, so that what happens to healthy people, who suffer from "frost-bite" when exposed to extreme cold, may also occur in people with a tendency to vasomotor spasm when exposed to milder degrees of cold. Usually the condition only extends so far as to produce blanching of the fingers, with numbing of the sensations, and sometimes severe pain. These symptoms may be brought on by washing the hands in cold water, or exposure of the hands to cold air. The vast majority of people, if not all, who suffer from this condition, are sufferers from some form of impaired health, probably toxic in origin. It will be found sometimes to supervene on recovery from some infective complaint, as influenza, malaria or dysentery. It is most frequently found associated with affections of the digestive tract, and is especially common in people with long-standing dilatation of the stomach from pyloric stenosis, and in these marked improvement may occur after a successful operation.

These milder forms of vasomotor constriction are allied to that mysterious complaint called Raynaud's disease. Here the contraction of the arterioles and the capillaries of the hand may be so persistent and extreme that the supply of blood to the fingers may be cut off and gangrene may result.

There are records of rare cases of this condition or of some condition allied to it, coming on with dramatic suddenness and resulting in the stoppage of the blood supply of a limb, followed by gangrene. One case observed by one of us (M) was of quite exceptional severity. The patient, a spare hard-working woman of 35, after walking a mile on a hot day, entered a house, and suddenly became conscious of a curious smell, and then cried out with pain in her legs and fell to the ground. She was put to bed and suffered greatly for a few hours. She could hardly move her legs and there was no pulsation in the femoral arteries. She lingered for 5 days. After the first few days the nails of the fingers, at their bases, on both hands were found to be black, due to extravasated blood underneath the nails. The urine was pink-stained. Opportunities were lacking for making a more thorough examination. The patient remained clear in her mind up to the day before she died. Signs of gangrene were setting in at the toes. The radial pulses were perceptible, but feeble.

At the post-mortem examination, not very efficiently performed, there was nothing wrong detected in the heart and other organs, except a large clot which blocked the abdominal aorta at its bifurcation. Seeing that the vessels of the fingers were affected as well as the kidney, there was more present than the blocking of the aorta would account for, and the suggestion occurs that a widespread contraction of the arteries, large and small, was the cause of the attack.

Treatment.—The vasomotor changes, dilatation and spasm, are invariably secondary, and to undertake a rational treatment requires a recognition of the primary disease. The detection of these phenomena should at once compel a search for the provoking causes, some of which have been mentioned, and treatment directed to their removal. When this is not successful we are compelled to adopt methods for the relief of suffering.

Throbbing of the arteries, with palpitation, is often very distressing and relief may be afforded in several ways. Frequently these sensations are accompanied by a sense of heat, especially in certain forms of exophthalmic goiter. Many of these patients get much relief from cold baths or sponging the body with cold water. The bromides, especially the bromides of ammonium, are often efficacious in cases of this kind. The drug should be pushed until a slight degree of apathy is produced, say 20 grains (1.3 grams) thrice daily. Its effect will be obtained in four or five days, when it should be stopped. If beneficial, it should be given afterwards in smaller doses so as to keep a slight effect for ten to fourteen days, when it should be stopped and resumed if there is a return of the symptoms.

For the treatment of the suffering due to vasomotor spasm there are a number of expedients, which may result in temporary relief. Best of all is warmth, applied to the cold extremity, or by the drinking of hot fluids. Vasodilatation by the nitrites occasionally gives transient relief. Thyroid extract sometimes has a more lasting effect. The application of a tight flat tourniquet around the limb above so as to occlude all the vessels, and left on for several minutes produces a reaction after its removal, so that there is a temporary dilatation of the vessels, but no permanent effect is produced. These are but temporary measures. The regulation of the clothing, if the patient lives in a cold climate, and the avoidance of exposure to cold, may help to render life less miserable. The drinking of hot fluids in large quantities in cold weather often helps, while living in a warm climate may avoid the conditions that cause the suffering. But these attempts at relief should never shut out from the physician's mind the necessity for finding the primary cause.

ARTERIAL BLOOD PRESSURE

An efficient circulation depends on the maintenance of a steady flow of blood in the capillaries at an equable pressure. The force that causes the flow is intermittent (the ventricular systole), and the conversion of the intermittent flow into a steady one is the function of the blood vessels. This is achieved partly by the elastic coat of the arteries, and partly by the modification of the caliber of the vessels by the branching and by the muscular coats. The force supplied by the ventricle is not entirely spent on the stream of blood during the systole of the ventricle but part of it is stored up in the elastic coats of the arteries, to be liberated during diastole, so that there is a pressure inside the arteries during diastole as well as during systole.

Before the invention of mechanical devices to measure the blood pressure the instrument by which the character of the pulse was ascertained was the fingers of the trained physician, and it is still by far the most reliable and sensitive of instruments. Behind it is not only an intelligent appreciation of the qualities of a pulse beat, but the knowledge acquired by long experience for the due interpretation of the sensations conveyed to the fingers.

Of recent years much attention has been given to blood pressure, and many instruments have been invented for the purpose of acquiring a more accurate knowledge of this subject. The more common procedure is to compress the brachial artery by encircling the upper arm with an air bag connected with a manometer. The pressure within the air bag is raised till the flow is stopped, and the pressure registered by the manometer at this period is described as the systolic pressure. The gradual return of the air in the bag permits the artery to expand, and at a stage, detected in various ways, the pressure at the end of diastole is supposed to be recognized. As a precise figure always conveys to the mind the conception of accuracy, the description of the blood pressure in terms of millimeters of mercury has led to the idea that this method of judging the character of the pulse is a distinct advance. Apart from the fact that there are characters and qualities in the artery and its contents which no instrument can reveal, it should be recognized that the figures given as the diastolic and systolic blood pressure are not really the true figures. It would take too long a time discussing an unprofitable subject to enter into detailed proof, but there is sufficient evidence to show that while the figures obtained do not represent the actual pressure, they are of distinct value as indicating approximately different degrees of pressure and are of a limited use in practice.

We are as yet far too ignorant of the factors concerned in the variations of arterial blood pressure to be able to make much use of them in practice. The use of the method in practice, before the significance of the results was understood, has led to mistaken lines of treatment and of prognosis, with the result that a means of investigation of value is being discredited.

The reason for referring to blood pressure instruments in this way is to direct attention to the urgent need of the more thorough study of this matter from a clinical standpoint, by the application of the principles which should govern clinical research. This is not the place to enter into these principles in detail, but it may be stated that they involve a thorough appreciation of the factors concerned in the production of the pressure and in causing its variations, the study of its peculiarities in health and in disease, and the watching of patients through long periods of years, with a recognition of the phenomena that may be associated with the varying changes in the pressure and in the disease process. This study requires that the blood pressure of individuals should be taken while they are in health, and at the outset of their disease, and at times during its progress. The need for this is at once apparent from the fact that hitherto high arterial pressure has been well established before it was detected, so that the circumstances that favored its onset are a matter of unintelligent guesswork.

It will be said that such an investigation is beyond the power of one man, seeing that the observer may not live long enough to complete his work. But this should be recognized and the basis laid whereby the investigation should be carried on by a series of observers. Until this conception of clinical investigation is recognized and acted upon, knowledge of blood pressure will remain imperfect and the results will be misleading.

Aneurysm of the Aorta

Definition.—In certain diseased states of the arteries the walls give way and produce enlargements to which now the terms aneurysm and dilatation are applied. By the latter term is meant a somewhat uneven enlargement of the channel of a vessel for a considerable length; by the term aneurysm is meant a comparatively abrupt enlargement of a more circumscribed tract. It is not always possible, clinically, to adhere to this distinction between dilatation and aneurysm.

Cause.—Aneurysms and dilatation of the aorta are caused by the pressure of the blood within the artery on walls which have been weakened by the progress of degenerative changes, or by the effects of injury. The pressure causes bulging at points in which the resisting power of the vessels is impaired. Apart from injuries, aneurysms of the aorta arise from the degeneration of the arterial walls, in the majority of cases of syphilitic origin. It is far more common in men than in females, and among men it is more frequent among those who lead a life calling for strenuous muscular effort.

The aorta, especially the thoracic portion, is the most commonly affected artery in the body. Very commonly the aneurysm begins in the region of the sinuses of Valsalva and involves the ascending part of the arch, being preceded by a syphilitic aortitis. In the diseased state, the walls of the arch lose much of their elasticity and give way before the shock of the blood thrown upon them with each ventricular systole. The resistant power of the middle and outer coats being lessened, the inner coat, not yet thickened as in atheroma at a later stage, gives way and the sac is formed. Other arteries sometimes affected are the popliteal, femoral, carotid, subclavian, axillary, innominate, iliac, cerebral and visceral. In the case of the cerebral, miliary aneurysms are not uncommon, especially in the arteries supplying the lenticulostriate body and the retina.

Aneurysms of the aorta may be fusiform in shape or sacculated. In some cases the coats cannot be traced, in others the media is much atrophied, while the intima may be thickened and atheromatous. Laminated clot may partially or completely fill the cavity in the saccular variety.

A dissecting aneurysm is one in which the blood has forced its way between the intima and the media, or between the layers of the media, due to an injury of the intima, or as a result of its destruction owing to degenerative changes. It generally arises from the cracking across of an atheromatous patch. The blood, stripping the coats, may find its way back into the blood stream. Cases of so-called "double aortae" are dissecting aneurysms. As the result of a wound, an artery may communicate directly with a vein giving rise to the condition called aneurysmal varix. Where the communication is less direct, perhaps winding through the intervening tissues, the name of varicose aneurysm has been used.

Symptoms of Aneurysm

It is rare that an aneurysm is discovered until it has advanced so far as to produce symptoms of pressure, and not infrequently its presence is unsuspected until it is revealed by an X-ray examination taken for other purposes, or at a post-mortem examination. One of the earliest signs in many cases is a pain, persistent and boring, referred to the back between the shoulder blades or over or below one shoulder blade. Occasionally pain is complained of in some other part of the chest or under the ribs. Even when the most careful physical examination is made no other symptom may be detected, but a persistent pain, in the chest or its neighborhood, should always call, where possible, for an X-ray examination.

An X-ray examination is undoubtedly the surest means of recognizing an aneurysm, but while it is an easy means of diagnosis, yet there are cases where the most skilled radiologist may have a difficulty in deciding whether the shadow revealed is that of an aneurysm or a growth. The pulsation of the aneurysm is not always perceptible, and the aorta may communicate a movement to a tumor in contact with it. There is one point in which precaution is called for, and that is in determining whether there is a small aneurysm of the arch of the aorta. In some radiographs the shadow of the aorta seems to show a rounded swelling which is not infrequently mistaken for an aneurysm. This is really due to the angle at which the photograph is taken, so that this appearance is due to the perspective and is a perfectly normal sign and is called by some radiologists the "aortic knob."

Clinically it is useful to divide the thoracic aorta into ascending, transverse and descending portions. The symptoms may conveniently be grouped into (1) the direct evidences of structural change (tumor growth), and (2) the symptoms evoked by pressure of the growing tumor on neighboring structures as evidenced by displacement of organs or interference with the function of the parts concerned.

Aneurysm of the Ascending Aorta.—When the aneurysm is small and close to the sinuses of Valsalva, there may be no sign. The aortic semi-lunar valves may be involved, and thus the cardiac signs obscure the aneurysmal. Anginal symptoms may be very prominent when the coronary arteries are involved. Occurring higher in the arch, an aneurysm may attain large size. Pulsation may be visible or palpable to the right of the sternum in the second interspace. Slight pulsation, detected in this area, should lead to a more careful scrutiny for other signs. In aortic regurgitation or in excitement such a pulsation may be seen, but it also involves the carotids and other arteries. In aneurysm the pulsation is more localized and dullness will be detected on percussion over the pulsating area. The dullness may be central and extend a little to the right and left of the sternum. Sometimes a thrill or a double thrill may be felt, the second corresponding with the second sound of the heart. On auscultation, a murmur may or may not be heard, occasionally a double murmur is heard. If the heart is hypertrophied and the semi-lunar valves competent the second sound may be accentuated.

When large the sac may erode the ribs and sternum. The superior vena cava is liable to be compressed and cause the veins of the head and arms to be distended, and the veinlets over the chest, particularly over the lower ribs on the right side, may become greatly dilated, and the flow of blood from the chest is then diverted and returns to the heart by the inferior vena cava. Pressure on the vagus may cause attacks of syncope. Rupture may take place into the pericardium, pleura or superior vena cava.

Aneurysm of the Transverse Aorta.—The growth is generally backward and downward. It may, however, grow forward and become obvious as a pulsating tumor. An area of dullness may be detected in front or behind near the spine. On pushing the finger deep into the episternal notch the pulsating aneurysm may be felt. Pressure symptoms predominate in this aneurysm. Even though small the sac, growing backwards, may press on the trachea or a bronchus. The trachea in the neck may be pushed slightly but definitely to one or the other side. The trachea may be jerked down with expansion of the sac (tracheal tugging). One or other bronchus, generally the left, may be obstructed by pressure from the sac, leading to collapse and inflammatory changes in the lung, a not infrequent cause of death in this condition. Hemorrhage from the sac weeping into the bronchus may precede a severe and fatal termination in this manner. Pressure on the esophagus or on the vagi may cause difficulty in swallowing. Rupture of an aneurysm from the passage of an esophageal bougie has caused death. Pressure on the left recurrent laryngeal nerve will give rise to paroxysmal dyspnea with stridor, sometimes the first indication of mischief. Later a peculiar brassy cough develops with paralysis of the adductors of the glottis. The voice is altered, becoming hoarse, weak or aphonic. Pressure on the sympathetic fibers leading to the neck, will cause at first dilatation of the pupil of the eye on the same side, followed later by contraction when the impulses are blocked.

When the aneurysm occurs after the innominate has been given off but involves the origin of the left subclavian artery, there may be a difference detected in the two radial arteries. This is usually described as due to a delay of the left radial pulse. As a matter of fact there is no delay but merely a diminished amplitude of the pulse wave, and the wave slowly increases in height, whereas the increase in height in the normal right radial is abrupt (see Fig. 1).

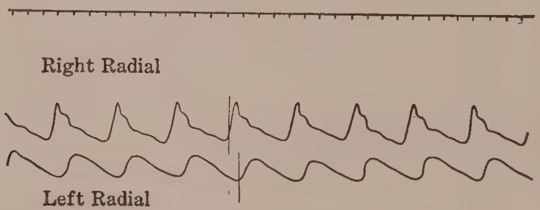

Fig. I.—Simultaneous tracings of the right and left radial pulses from a case of Aneurysm of the arch of the aorta beyond the innominate but involving the origin of the left subclavian artery. The pulses felt unequal, but the records show this was synchronous. The pulse of the right radial reaches its full height suddenly, while the left pulse reaches its height gradually. The systolic pressure in the right radial was 130 mm. Hg., in the left 110 mm. Hg.

Aneurysm of the Descending Aorta.—Many of these pass unnoticed and are revealed only by the X-rays, or at the post-mortem. In some the tendency is for the dorsal vertebrae to become eroded. The spinal cord may be compressed. Agonizing pain may be felt, shooting round to the front on one or both sides, accompanied by herpes zoster or hyperesthesia due to pressure on the nerve roots. The lungs and esophagus may be compressed. Hemorrhage into the lungs may occur, resembling the hemoptysis of phthisis pulmonalis. Rupture may take place into the pleura or esophagus.

Aneurysm of the Abdominal Aorta

Aneurysm may occur in any part of the abdominal aorta or of its branches within the abdomen. While of moderate size they may be recognized as pulsatile tumors. In thin persons it is easy to mistake a pulsating aorta for an aneurysm. A tumor such as occurs in carcinoma of the stomach may easily be mistaken for an aneurysm. Various expedients should be resorted to in order to be certain of the nature of the tumor, as pushing it to one side, grasping it as a whole to see if it pulsates. Another useful method is to get the patient to kneel on his elbows and knees, and observe if the tumor falls away from the aorta and ceases to pulsate.

Abdominal aneurysms tend to become very large and to press upon the other abdominal organs and to cause erosion of the vertebrae and other bones with which they come into contact, so that the variety of symptoms to which they can give rise is very great. When they rupture, they may do so into the hollow viscera, the peritoneal cavity, the spinal cord, and so many other places that one almost never detects two cases bursting alike.

Prognosis in Aneurysm

There is no rule which one can follow as a guide in prognosis in all cases, as the outcome of an aneurysm may result in death soon after the recognition of the condition, or the patient may live many years scarcely embarrassed. It should be borne in mind that the aneurysm may have been present for many years before its detection. In every case judgment should be suspended for a few months to see if the condition is progressive or amenable to treatment. In many cases where the aneurysm is found bulging out the chest wall, after a period of rest it may diminish in size, and the patient be able to get about his affairs and lead a useful life for an indefinite number of years, and when he dies, he dies not because of his aneurysm but from some intercurrent complaint. It often happens that aneurysms of various sizes in the descending aorta are not recognized until a post-mortem examination has been made, the death not being due to the aneurysm. It must always be remembered that changes similar to those which have affected the aorta may have affected the coronary arteries; the patient's weakness and suffering may be the outcome of the cardiac condition and not of the aneurysm. Indeed, it not infrequently happens that patients with aneurysm suffer from angina pectoris, and die from cardiac exhaustion. On the detection of an aneurysm there is a tendency to attribute the danger and suffering to the aneurysm and not to the heart. When, in spite of rest, the aneurysm continues to increase in size, then the patient drifts to death, the cause of death, however, being due more often to exhaustion than to rupture.

Rupture of aneurysm is such a tragic occurrence that it is this that is often feared after the detection of an aneurysm. It is, however, a comparatively rare event, for the great majority of aneurysms do not rupture. When they do rupture it is usually an unexpected event, and generally it is into the bronchi or lungs, and in abdominal aneurysm under the peritoneum. Some of these rupture at an early stage before time has been afforded for the wall of the aneurysm to be supported by the consolidation of the surrounding tissues. It is therefore incumbent on the physician to watch carefully for any signs of extension after the detection of the aneurysm, either by percussion or by the X-ray. Another sign of approaching danger is blood-stained expectoration. In one case an aneurysm, revealed only by the X-ray, at the arch of the aorta on the left side, was so small in size that there was some doubt as to its nature. The sputum was, however, blood-stained, and a few days later a slight dullness to percussion indicated an increase in the size of the aneurysm, and a few hours afterwards the patient suddenly coughed up some blood and expired.

The basis of a prognosis depends on the rapidity of growth and the involvement of structures necessary to life by the pressure of the growing tumor. Such signs as attacks of dyspnea and blood-stained expectoration give grave warning. On the other hand, the absence of any serious signs of pressure and the cessation of growth are, on the whole, evidences for a favorable prognosis.

Treatment of Aneurysm

Principles of treatment are based on the fact that while the immediate cause of the aneurysm is disease of the wall of the aorta, the heart's force is the true cause of the increase in the size of the aneurysm. The damage to the wall cannot be made good and it is to be hoped that the wall may be strengthened by the deposit of clot on its interior. The heart's force is diminished by rest, and the formation of clot is favored by a quiet circulation. As bodily effort increases the heart's force, it is manifest that the best line of treatment is rest, so that, so long as there is evidence of the aneurysm increasing in size, rest must be assured. When after some months there is no evidence of increase, the patient may be allowed to get up and gradually get about his affairs, provided these do not involve much bodily exertion.

When the aneurysm is the chief source of danger, there is often a good deal of suffering, and the pain may be taken as a guide. Thus with rest the pain disappears in most cases. When the patient gets up and goes about, so long as the pain does not return it may be taken as an evidence (in the absence of any other sign of increase in size) that matters are favorable. A return of the pain calls for a diminution or a cessation of effort.

In this matter it is always necessary to make certain that the pain and weakness are not cardiac in origin. As cardiac pain and the signs of cardiac exhaustion are very definite, little difficulty should be experienced in recognizing the purely cardiac symptom. (See sections on Heart Failure and on Heart Pain (Angina Pectoris) in Vol. II, Chap. XIII.)

A great many expedients have been used to facilitate the formation of the clot and for influencing the course of disease. It is doubtful if any of these are of value. It is possible that a diminished diet may help, though there is little reason for resorting to the extreme that Tufnell and others have adopted. When it is realized that the aneurysm in many cases has existed for years before its discovery, and that many people lead useful lives after it has been discovered without any special restrictions beyond those I have indicated, it can readily be seen that cases that have been treated by some special method may do fairly well. It is, however, not justifiable to attribute the improvement to the special method unless some demonstrable result of the treatment can be shown.

Where syphilis is the cause of the aneurysm, anti-syphilitic treatment is usually recommended. But except on a general principle (of doubtful value) that all syphilitic cases should be so treated, it is difficult to see what good this kind of treatment can do. When pain is a persistent and distressing symptom, the careful administration of sedatives is called for. Certain drugs as the iodides and arsenic have been recommended as useful agents to prevent the growth of the aneurysm or in relieving the suffering; it is doubtful if they have any effect; probably the improvement that follows rest has been credited to the drug.

DILATATION OF THE AORTA

As dilatation of the aorta is generally a much milder affection than aneurysm, a few words are necessary to appreciate the difference. In many people with advancing years the arteries become large and tortuous. The same processes that produce these changes in the arteries in general affect the aorta, and we get in consequence a general dilatation of the aorta. Dilatation of the aorta is also frequently present in aortic regurgitation, particularly in those cases where there is a high systolic blood pressure and a very low diastolic. The force with which the blood is thrown into the aorta is undoubtedly the chief factor in producing this dilatation. With extreme weakening of the walls of the aorta the dilatation may be so great that it should be considered among the aneurysms.

Symptoms and Signs of Dilatation of the Aorta.—The symptoms as a rule are very few and the signs are practically limited to a slight dullness over the manubrium sterni and the detection of pulsation in the episternal notch. The X-ray is the best means for revealing its presence. It rarely produces pressure symptoms.

Prognosis.—No grave consequence is likely to result from a dilated aorta. It rarely causes trouble because of mechanical pressure. It rarely, if ever, bursts. The worst that happens is that it interferes with those peculiar features of the aorta that favor the flow of blood, chiefly by abolishing the effects of the elastic coat, and thus tends to embarrass the heart in its work, which is itself usually impaired in consequence of changes in the coronary arteries. No prognosis should be based upon the detection of a dilated aorta, especially in the milder degrees. This caution is needed, for its detection by the X-ray not infrequently has been the cause of unnecessary alarm.

Treatment.—As the dilated aorta is the outcome of a process that has been going on for many years, and which, in the nature of things, is irremediable, no time and energy need be wasted in attempts at treatment. If there are evidences of cardiac inefficiency, that should be the object towards which treatment should be directed.

CHAPTER XV

DISEASES OF THE BLOOD

THE PATHOLOGICAL PHYSIOLOGY OF BLOOD CELL FORMATION AND BLOOD CELL DESTRUCTION*

BY CECIL K. DRINKER

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BLOOD FORMATION

In 1868, Neumann[1] discovered nucleated red cells in bone-marrow. His discovery initiated modern hematology, a field in medical science which has been tilled first by the histologists and embryologists, and then by the pathologists and physiologists. But in spite of an enormous accumulation of work bearing or purporting to bear upon the ultimate origin of the blood-cells, upon the transformation of nucleated red cells into their non-nucleated condition, and upon other obvious questions, the harvest of useful information at the disposal of the clinician is not large and is so mixed with the chaff of poor research and misleading terminology as to be available with comparatively great difficulty.

The interest of the clinician in the fundamental problems of blood formation and destruction receives daily stimulation from his experience with diseases characterized by a preponderance of one or the other of these factors. His interest causes him to ask concerning all such cases, "What is the reason for this blood picture?", or in the presence of other suggestive symptoms, "Why is the blood picture in this individual still undisturbed?" It is safe to say that the best success in the modern diagnosis, prognosis and treatment of anemia and allied conditions rests upon answers to these questions. We are unfortunate in our inability to study diseased blood-forming organs directly but must always deduce their condition through the blood picture, the history and symptomatology of the case. In making such deductions the physician requires first of all an interpretative knowledge of the literature upon blood formation and destruction, and must couple this with direct experience in the blood diseases.

THE BLOOD-FORMING TISSUES

A. Formation and Character of the Erythrocytes

The infant at birth shows active blood formation in several organs. The condition of the well-developed embryo is reflected in the presence of active erythrogenetic islets in the liver. The spleen and other lymphatic tissue with almost equal constancy show similar areas, but in both cases the formation noted is a reminder of what has been and not a forecast of future conditions. In relatively few months after birth the red bone-marrow has entirely absorbed the erythrogenetic function and in adult life is practically the only source of formation. Until about the sixteenth year red marrow fills all the bones, but after this time it is confined to the flat bones, the small spongy bones and the heads of the long bones. As a result of blood destruction all of the localities, presenting blood formation in the infant, may become active once more, but in this connection it should be noted that the liver only does so under extreme need, while the spleen may become an active site of blood formation from far less cause. Meyer and Heineke[2] and Draper[3] have reviewed the question of the tendency for resumption of the regenerative process by the liver and spleen, and have shown that the former organ is not apt to present activity unless the anemia is very severe. Schridde[4] has also shown that regeneration in the liver is rarely found as a result of secondary anemia due to hemorrhage. The greater frequency of resumption of regenerative power by the spleen has been responsible for the idea that islands of blood formation are metastatic in character, the result of transfer of young cells from the red marrow in times of extreme regenerative activity, the cells in question being filtered out in the spleen. It is, however, more probable that the resumption of activity is due to the presence of hemoblastic cells which, in the absence of extreme stimulation, have been quiescent. Wherever mammalian red blood-cell formation is found the fundamental tissue involved is a single entity. Stockard[5] has emphasized this fact, and its truth is borne out no matter how far back we go in our studies of embryonal mammalian blood-forming tissue. We are dealing with a single organ, the final structure of which has proved too delicate for perfect description but which is so similar wherever found as to admit of no doubt concerning its unit character.

To have successful red-blood formation, a fine reticular tissue pierced by wide sinusoidal vessels of extreme tenuity of wall is required. Clusters of red blood-cells lie apparently outside the direct blood channels through which the blood flows freely. Whether or not the sinusoids of the bone-marrow possess intact endothelial walls is a matter of debate upon which investigators are about equally divided. The question is one of practical importance when intelligent effort is made to understand the mechanism of the normal or abnormal blood picture. Van der Stricht[6], Dominici[7], Brinckerhoff and Tyzzer[8], and Rindfleisch[9] believe the walls of the sinusoids are quite incomplete, permitting blood to wander freely from the vessels into the reticulum and providing in this way for ready delivery of erythrocytes into the circulation. Langer[10], in a very extensive study of the vascular system of the bone-marrow, contends that the vessels are intact structures as in the case of other capillaries. Hoyer[11] holds the same view, and C. S. Minot[12] remarks that, "Certain investigators assert that the cavities of the blood-vessels are in direct open connection with the spaces of the mesenchyma, but, so far as I know, the conclusive proof of the correctness of this statement is lacking."

As a result of a variety of experiments[13] it is possible for the author to assert that both open and closed vessels exist in the bone-marrow. Under certain conditions the vessels communicate freely with the blood-islands in the reticulum, but there is a constant tendency toward an intact system, and it is probable that in the healthy adult the vessels are always closed and are quite comparable to capillaries in other parts of the body save for their greater diameter. This latter feature is very characteristic and insures an extreme slowness of blood flow. Leading into these wide capillary spaces, called sinusoids, are small arterioles which in all cases are apparently well supplied with vasomotor nerves[14]. Other nervous filaments are distributed through the blood-forming tissue outside the vessels[15]. It would seem that these nerves must be afferent in character[14] but their function—indeed, the whole question of possible nervous control of the cellular secretion of blood-forming tissue—is an almost unexplored field. Outside the capillaries there is an extremely delicate reticulum attached both to the walls of the capillaries and to the fat-cells which are often conspicuous in the bone-marrow. In the reticulum we find masses of cells giving rise to the different formed elements found in the circulating blood together with adult blood-cells. (The reader wishing to familiarize himself with the manifold shapes, sizes and staining characteristics of marrow-cells is referred to the monograph of W. E. Carnegie Dickson[16], The Bone-Marrow, which in our estimation is the best atlas upon the bone-marrow and the blood so far prepared.)

The Cells of Red Blood-Forming Tissue

1. *Hemoblasts.*—These are mononuclear cells about the size of polymorphonuclear leucocytes or slightly larger. They possess large nuclei containing a wide reticulum which shows a few thickenings of varying sizes and irregular distribution. The cell-body is irregular in form and stains a darker blue with methylene-azure-eosin stains than does the nucleus.* In very good preparations these cells may occasionally show very fine granules in the cytoplasm but ordinarily they are granule-free. Such elements are found now and then in the circulating blood and always cause confusion. They are wrongly classified as myelocytes, large lymphocytes, or by the more ambitious as erythroblasts, myeloblasts, or lymphoblasts. It is, however, safer to include such cells under the general designation of *hemoblasts*. We are not sure as to their origin and are equally in doubt as to what type of cell any individual of this variety will produce. These cells are often markedly increased in the bone-marrow in long-standing leucocytosis, in which case they are evidently concerned in leucocyte formation[16]. We have seen them very numerous in the blood in secondary

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* Wright's stain is a good example of this group.

anemia. Only one fact is certain and important for the clinical hematologist anxious to classify cells of the type under discussion. They are extremely primitive forms, and their presence in the circulating blood in any number indicates floridity of blood formation, decidedly abnormal.

2. *Hemoglobin-Containing Cells.*—These vary in size as they are found in the bone-marrow, but the conditions observed are probably not different from those found in younger embryos, where one readily notes that, "the erythrocytes differ much in size. In later stages, as in the adult, we find that the developing erythrocytes are much more uniform. From these relations we draw the conclusion that during the developmental period both larger and smaller mesameboids", (the hemoblasts described under 1), "transform themselves directly into colored corpuscles[17]."

The cell containing even the earliest traces of hemoglobin is usually easy to recognize since this substance causes a homogeneous coloration of the cytoplasm, bluish green when stained with Wright's stain. A division of young red cells is usually made upon the basis of size.*

(*a*) Megaloblasts: These are large forms containing varying amounts of hemoglobin and a nucleus which varies from a loose reticular structure carrying occasional knots of bluish black material to a solid black mass. The form of the nucleus may be quite round, in which case it is usually eccentric in position, or it may take a variety of bizarre shapes. It was the contention of Ehrlich, and he has been followed by a group of German hematologists[18], that megaloblasts do not occur in normal regenerating bone-marrow. While it is probably true that they are absent in healthy adult marrow, they are very easy to find in the marrow regenerating actively after hemorrhage, and it is not possible to contend that their appearance in the marrow or in the peripheral blood stream indicates a pathological reversion to embryonic conditions. Megaloblasts have been found in the circulating blood in all forms of severe anemia provided regeneration is vigorous, and their discovery in blood smears is no proof of pernicious anemia.

(*b*) Normoblasts: These are nucleated hemoglobin-containing cells of the same size as normal erythrocytes. They are the most numerous of the nucleated red elements. They may vary in their hemoglobin content and in the shape and solidity of their nuclei just as do the megaloblasts, but most commonly they show a single round or oval nucleus very dense and black, eccentrically placed, and a cytoplasm as well colored with hemoglobin as in the case of the adult erythrocytes.

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* The term "erythroblast" appears frequently in the literature As originally used "erythroblasts" were colorless cells destined to form red cells, but clinicians have applied the term to all types of definite nucleated red cells. We can see little need for such a word and pass in our classification from the undifferentiated hemoblast directly to nucleated red corpuscles containing unmistakable hemoglobin and varying in size.

(*c*) Microblasts: These are simply smaller forms than the normoblasts and possess no other distinctive characteristics.

There is no evidence that these different sizes of nucleated cells are genetically related to one another. That is, the megaloblast is not the parent of the normoblast and so on. The steps by which any of these nucleated elements form adult non-nucleated cells have been much in debate. Kölliker[19] was the first advocate of solution of the nucleus within the cell. Rindfleisch[9] believed the nucleus was extruded. Jolly[20] has reviewed the entire discussion up to 1907 and concludes that, while karyolysis may occasionally occur under embryonic conditions, it is rare after birth. The expulsion of the nucleus is to be regarded as the normal process, the expelled nuclei and nuclear fragments being eaten by phagocytes[21] and therefore appearing but rarely in the circulating blood, unless blood regeneration is very rapid, when one often finds unmistakable naked nuclei in the blood stream. Bunting[22] has called attention to their presence as a result of ricin and saponin administration, both of which substances cause marrow breakdown. It is possible that their appearance in the blood stream may mean not only rapid red-cell division but also cellular disintegration. Juspa[23] has described the loss of the nucleus as a result of ejection of chromatin into the cytoplasm. His observations were made upon human blood in anemia. It is probable that the "Ring Bodies" described by Cabot[24], the particles known as "Howell-Jolly Bodies[25]," and other small fragments seen in the cytoplasm of red cells and distinct from basophilic granulation are all nuclear fragments. A peculiarity which has been frequently noted in relation to the Howell-Jolly nuclear fragments is the frequency with which they are found in the blood after splenectomy[26]. At present no explanation for this phenomenon can be given.

Emmel[27] studied the nucleated cells of embryonic pigs' blood and found them capable of dividing mitotically and by a process of budding and gradual constriction. In this latter instance the daughter cells were non-nucleated. Emmel's paper reviews the literature on red-cell division up to 1914. More recently Tower and Herm[23], studying cultures of red bone-marrow, describe the formation of non-nucleated cells as follows: "It was early found that the modern explanation of the formation of the mammalian red blood corpuscle did not agree with the activities observed in the cultures and that instead of witnessing a normoblast remodeled into a non-nucleated corpuscle by losing its nucleus we saw this same normoblast sending out unnucleated straw-colored bladders from its nucleus, these bladders finally separating off as true red corpuscles." R. Erdmann[29] has criticized this observation, since cells of all types in tissue culture tend to bud and divide rapidly. As a consequence, the process described by Tower and Herm[28] may not be the rule in normally placed tissue.

Omitting a discussion of the large volume of work which surrounds the questions of nuclear absorption or nuclear extrusion, we may emphasize two facts: first, that formation of new red cells requires a nucleus; we know of no reports giving evidence that non-nucleated red cells divide; second, each nucleated cell seems to be capable of producing several other cells whether nucleated or non-nucleated, and the processes involved take place to best advantage in red cell-forming tissue such as is typified by the bone-marrow. It is not surprising, therefore, to gain evidence that the organism loses nucleated red cells from the marrow only under considerable stress and that this loss is rarely of long duration[13]. The hemoglobin content of nucleated red cells, judging from their reaction when stained with Wright's stain, varies in some way, in that the hemoglobin-containing cytoplasm may present a variety of shades from light greenish blue to the orange red characteristic of ordinary erythrocytes. It is unknown whether red cells can modify their hemoglobin content in the absence of the nucleus. The synthesis of this compound indicates the need for chemical reactions in the blood-cell which we ordinarily fail to associate with it, being concerned only with study of its most prominent function, the transport of oxygen and carbon dioxide to and from the body tissues.

In 1910, Warburg[30] showed that the metabolism of the nucleated circulating blood-cells of the goose was much greater than that of the non-nucleated circulating blood-cells of man. The latter, however, were living entities using oxygen but in extremely small amounts. Morawitz[31] studied the metabolism of the blood of anemic animals as contrasted with normal animals and found a marked difference. The blood of the anemic animals had a very considerable metabolism. When these experiments were carried further by Morawitz and Itami[32] and were correlated with the histology of the blood, it was found that the number of nucleated cells in the specimens would not account for all of the increase in metabolism found in anemic bloods. It must be due, in these mammalian bloods, to the number of young non-nucleated elements which they contained.

We are not as yet able, owing to the difficulty experienced in separating different types of red cells, to show a gradual decrease in the metabolism of the red cells as we pass from the nuclear to the adult non-nuclear stage. All we can say is that the blood of anemic animals containing many young forms metabolizes at a higher rate than does normal blood, and that this cannot be accounted for by the presence of nucleated red cells alone. It is, therefore, proper to suppose that after the loss of the nucleus the immature red cell continues processes bringing it toward its normal adult condition, and it thus becomes possible to consider that cells with no recognizable nucleus, in the ordinary sense of the word, may form hemoglobin and carry on other processes leading toward their adult state.

Morawitz and Itami[32] used another criterion in their judgment, as to the number of young forms in the bloods in which they were studying oxygen consumption, namely polychromatophilia. It is well known that anemic bloods—and this is particularly true in anemias following hemorrhage—at the time or just following the appearance of great numbers of nucleated red cells, will show many, frequently countless numbers, of non-nucleated cells staining bluish with Wright's stain. These polychromatophilic cells are apparently the descendants of nucleated elements whose cytoplasm is in an equal state of immaturity and which in the great speed of the regenerative process lose their nuclei abnormally soon. Krumbhaar[33] expresses the view that polychromatophilic cells are degeneration forms, but we believe they are unquestionably young cells, and it is doubtful whether there is any better, easily attained, single index of normal vigorous blood regeneration than pronounced polychromatophilia.

Owing possibly to the difficulty of estimating numbers of polychromatophilic cells, Morawitz and Itami[32] were unable to find a parallel between their appearance and oxygen utilization. In recent years, however, histological investigation has furnished another link in the chain leading from the nucleated red cell to the erythrocyte. This is the so-called reticulated red cell. In 1897, Benda[34] used the term "mitochondria" to indicate certain granulations in the cytoplasm of cells concerned in spermatogenesis. Mitochondria had previously been seen and have been given many other names. From 1900 until the present day, these bodies in the cytoplasm of cells have been the objects of vigorous attention on the part of histologists. With the exception of adult erythrocytes, they are found in all the cells of the human body. They are an essential accompaniment of the nuclear condition and are of importance to us in red cells since they disappear as these cells reach the age at which they normally function. Since the mitochondria of nucleated and young red cells are frequently strung together in skein-like arrangements, the cells showing them have been designated reticulated red cells. It is clear, however, that this reticulum simply represents in the red cell what we may see equally well in the leucocytes, lymphocytes, and indeed in all body cells. In the non-nucleated red cell, the demonstration of mitochondria, either as separate granules or as a reticulum, indicates proximity to the nuclear condition.

It is not possible to stain reticulated cells with ordinary blood stains. In order to demonstrate them a drop of fresh blood is placed upon an absolutely clean slide and one or two drops of Janus Green (1:2,000 aqueous solution made up to 1:10,000 with physiological salt solution for each experiment) are allowed to flow upon it. It is unnecessary to mix the blood and stain. The preparation is quickly rimmed with vaseline and examined after allowing five minutes for the corpuscles to settle. Other stains demonstrating mitochondria when used *intra vitam* are diethyl-safranin, cresyl blue, Bismark brown, pyronin, thionin, neutral red, gentian violet, nile blue, dahlia, methylene blue B.X., new methylene blue N., methylene 2 B. and Erhlich's rectified methylene blue[35]. Cresyl blue has perhaps been the favorite dye in demonstrating mitochondria for clinical purposes.

Robertson[36] gives the following method for staining and counting reticulated cells: "A saturated solution of brilliant cresyl blue was made up in normal salt solution. This was kept as a stock solution. When a count was to be made, a small quantity of it was diluted 80 times with normal salt solution and mixed with blood in a pipette for counting white cells in the proportion of one part of blood to twenty parts of cresyl blue solution. The mixture was shaken in the pipette for five minutes. The cells were then equally distributed as well as stained. They were counted at once in fresh preparations which were sealed with vaseline to prevent disturbances due to drying. At least 1,000 red cells were counted at each test."

Since different stocks of cresyl blue vary, it is necessary to find the proper staining dilution for each saturated solution. A few experiments will determine this and, once attained, the standard dilution may be adhered to. The simplest method for observation of reticulated cells is as follows. A drop of 1-300 aqueous solution of cresyl blue is placed upon a slide and allowed to dry. These slides prepared with cresyl blue are kept in stock and a drop of fresh blood simply placed upon the stain and a cover slip quickly adjusted and rimmed with vaseline. The stain will be taken up quite rapidly and a thoroughly good preparation will be secured. With a little experience, one gains a fair knowledge of the numbers of reticulated cells from such preparations. In the blood of healthy adults, reticulated cells are practically absent. Minot and Lee[37] find them present normally in the proportion of about 0.8 per cent. of the total red cell count. They increase markedly in anemia if regeneration is rapid, and indicate in a very reliable way the vigor of the regenerative process. Hawes[38] has brought out the fact that, owing to the delicacy of the vital staining method, the reticulated forms will always be found in considerably greater percentages than polychromatophilic cells. This is a statement which we can endorse very heartily. If blood smears are well made and well stained, polychromatophilia is of course noted if present. Advantage should, however, be taken of the great simplicity of the dried stain cresyl blue method we have given, since by means of it one gains a so much more reliable estimate of the activity of blood regeneration.

The uniform presence of mitochondria in the cytoplasm of the body-cells indicates the performance of some very common and indispensable function by these elements, but what this function is we do not know at the present time. (For a thorough summary of the structure and functions of mitochondria see E. V. Cowdry[39].) They are apparently associated with the active growing life of the cell. In the red blood-cells we have structures which perform their vital functions of gas transport when senescent. They become specialized carriers of oxygen and carbon dioxide, and when most useful in these respects are least expensive to the body. It will be remembered that Morawitz and Itami[32] were able to show increased oxygen consumption by the blood of anemic animals, but that their attempts to correlate this with the number of nucleated or polychromatophilic cells present were unsuccessful. Very recently Harrop[40] has examined the oxygen consumption of erythrocytes and has correlated this physiological measurement with the histological enumeration of reticulated cells, using Robertson's[36] method. His results are extremely interesting:

"1. Normal mature human erythrocytes have no oxygen consumption measurable by present methods.

"2. Where it is measurably increased in the blood of individuals with anemia, the oxygen consumption has no relation to the severity of the anemia and no constant relation to histologic abnormalities in the erythrocytes other than increases in the number of reticulated cells.

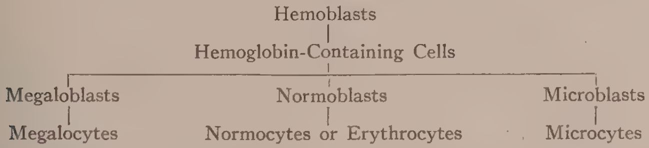
"3. Blood which contains abnormal numbers of reticulated erythrocytes has an oxygen consumption proportional to the percentage of reticulated cells present.

"4. The data afford evidence that the two phenomena go hand in hand. Both are due to the presence of abnormal numbers of youthful cells, and both are probably rather accurate indicators of functional variations in the bone-marrow, and the amount of blood regeneration."

Masing[41] has given a further method for detecting active blood formation by demonstrating an increase in nuclein phosphorus in the blood of animals regenerating actively after hemorrhage. So far this observation has not been confirmed.

Just as in the case of polychromatophilia, the bone-marrow will show reticulation in all types of nucleated red cells and in young non-nucleated cells. It is absent, however, in the later stages of red-cell existence. In addition to the diffuse polychromatophilia which we have discussed, a constant finding in blood-forming tissue is cells having the same basophilic tendency but in a punctate manner. These are the "stippled cells" so common in the blood of lead poisoning, but found in the blood in all anemias and constant constituents of the bone-marrow. They are cells whose cytoplasm shows distinct bluish black granules when stained with Wright's stain. These granules are not mitochondria and their genesis and functional significance are uncertain. Cadwalader[42] has reviewed the literature in regard to basophilic granulation and considers these particles to be nuclear fragments.

It is now possible to summarize red-cell formation in the following table:



All hemoglobin-containing cells except megalocytes, erythrocytes and microcytes, which have reached adult condition, may exhibit diffuse polychromatophilia and reticulation. Punctate polychromatophilia or stippling is sometimes seen in red cells, both nucleated and non-nucleated, whose cytoplasm is otherwise quite normal in appearance.

The manner of origin of hemoglobin is a matter which naturally comes under consideration as we discuss the finer structure of the red cells. The adult cell apparently consists of a delicate, extensible, colorless stroma in which the hemoglobin is carried. It has been held that hemoglobin is formed from special granules appearing early in red-cell life. Ciaccio[43] and Meves[44] have advanced the view that the red-cell mitochondria are concerned with hemoglobin formation, a view which obviously correlates the appearance of hemoglobin with the disappearance of reticulation. Schridde[45] has gone even further by declaring that mitochondria are directly transformed into hemoglobin. Direct observations supporting either of these views are at present lacking. At the present time it seems best to consider that the hemoglobin appears diffusely through the red cells and that proximity to the nuclear condition is necessary for its formation. It is unknown whether adult red cells poor in hemoglobin, such as we see in chlorosis, can increase their hemoglobin content. Stewart[46] has produced evidence that normal red cells do not take up hemoglobin from the surrounding serum. Most probably, therefore, the betterment which follows iron administration in this condition signalizes the development of a new race of cells, the old and impoverished race being thus replaced rather than improved.

If blood is taken from the body and slowly diluted with distilled water, hemolysis eventually occurs. With normal blood-cells hemolysis begins in about 0.42 per cent. solution of sodium chloride in distilled water and is complete in 0.28 per cent. sodium chloride. Unfortunately such tests of "fragility" are unsatisfactory in so far as they relate to blood regeneration. Bloods filled with young red cells show hemolysis in varying concentrations of sodium chloride, and the alterations observed are apparently referable to other causes than the age of the cells. Butler[47] covers the field quite thoroughly and instances certain diseases in which alterations in fragility do occur.

B. Formation and Character of the Granular Leucocytes

As has been suggested in our discussion of the hemoglobin-containing cells, the final cell giving origin to the red and white blood elements is so undifferentiated as to make it impossible to foretell what type of daughter cell will be produced. The origin of the adult blood-cells has been a matter of vigorous debate, one school holding that red cells and leucocytes develop from separate series of cells, another that they have identical parentage. As the matter now confronts the clinician, the following view seems the best one to be followed. In the blood stream and in smears from the bone-marrow in many instances of grave anemia and leukemia, cells will be found which, if viewed alone, cannot be identified safely as belonging to either the red or the white series. A preponderance of definite myelocytes, lymphocytes or nucleated red cells permits us in such instances to classify these indeterminate hemoblasts with the cells they will eventually form. We may, under certain circumstances, identify these cells as myeloblasts, but when we do so it is because the general blood picture at the moment forces us to this conclusion and not because we have a thoroughly safe histological entity under the microscope. Their presence in the peripheral blood is of the greatest importance in that it indicates an extremely vigorous production of the type of cell dominating the blood picture at the moment of discussion. It is of course quite probable that these hemoblasts, which we cannot differentiate into any special class of blood-cells except through their companions in the smear under consideration, have differences. But in terms of staining properties and physical characteristics we cannot appreciate these differences at the present time, and we consequently omit such fine-drawn discussions of myeloblasts, etc., as are often found, and pass directly to:

1. The Granular Leucocytes.

a. Neutrophilic Myelocytes: These are the most numerous cells found in the bone-marrow. They are usually slightly larger than the adult polymorphonuclear leucocyte and show granules of varying size. The nucleus is large and round or oval. It stains a rather light blue with Wright's stain.

b. Neutrophilic Polymorphonuclears: These are the common white corpuscles of the blood and require no description.

c. Eosinophilic Myelcytes.

d. Eosinophilic Polymorphonuclears: The eosinophilic leucocytes (myelocytes and polymorphonuclears) form a very distinctive group, not only from their appearance but also from the reactions in which they take part. The question as to the source of their peculiar granulation has been much discussed. Brown[48] observed that the muscle fibers of man invaded by Trichina spiralis become granular in the neighborhood of the parasite and that eosinophilic leucocytes are very numerous in areas of marked degeneration. He could not see direct ingestion of muscle substance by these cells but suggests it is possibly taken up in soluble form and then transformed to eosinophile granules. Brown's finding [48] that in cases of trichinosis the percentage of neutrophils in the blood fell as the eosinophils rose would seem to indicate such a transformation. Opie[49], however, calls attention to the fact that the marrow in animals with eosinophilia is very rich in these cells. It would seem that proliferation occurs in response to a special need and that no transformation occurs. That eosinophile cells produce other cells of similar granulation has long been known [50], but mitoses have never been found except in cells in the bone-marrow and in the blood stream of leukemic patients.

Weidenreich [51] believed the granules to be hemoglobin, the product of degenerated erythrocytes. Badertscher[52] has made some most significant observations on the eosinophililc leucocytes of an amphibian, Salamandra Atra. In these animals during metamorphosis a marked degeneration of both muscle tissue and erythrocytes takes place. Some of his conclusions are as follows:

"1. The eosinophile granules are exogenous in their nature, that is they are derived from material outside of the cell containing them and not directly a product of the activity of the leucocyte itself. The presence of free eosinophile granules found to be so plentiful among degenerating erythrocytes and muscle tissue and later taken up by lymphocytes, supports this conclusion.

"2. The eosinophile granules are products of degenerated muscle tissue and degenerated erythrocytes. This is supported by the fact that they are found only in connection with the above named degenerating tissues. The fact also that more eosinophile leucocytes are found in the blood during the period of metamorphosis than in the larval or in the adult condition, supports this conclusion.

"3. As they are found only in connection with tissue containing a relatively large amount of hemoglobin, it is believed that hemoglobin is part of their chemical composition. This conclusion by no means excludes the probability that the eosinophile granules contain chemical compounds besides hemoglobin.

"4. The eosinophile granules are taken up by the lymphocytes (large and small) which are thus converted into eosinophile cells. The eosinophile leucocytes are, therefore, the white blood cells ingested with the products of degenerated erythrocytes and degenerated muscle cells.

"5. The eosinophile cells with different types of nuclei are genetically related to one another."

The cells called "lymphocytes" by Badertscher are small undifferentiated elements which, however, pass by regular stages to a polymorphonuclear state. Attempts have been made to show that the neutrophilic leucocytes undergo gradual transformation to eosinophilic forms. At present, however, we may best believe that undifferentiated cells exist which are concerned with removal of degenerating hemoglobin-containing tissues. These cells are capable of subdivision and undergo a gradual nuclear transformation until the adult polymorphous condition is reached. Like the basophilic leucocytes the eosinophilic cells are more tissue than circulating elements, and only occasionally reach the blood stream in numbers. While such a statement gives us understanding of eosinophilia in trichinosis, it does not give any clue to the eosinophilia of such conditions as bronchial asthma and the increased numbers of these cells in the lung tissue and the bone-marrow in this disease. It should be understood that the property of staining with eosin cannot be finally identified with iron content of granules. Many widely different tissues may have similar tinctorial properties but differ fundamentally in character. It is thus possible that the eosinophilic leucocytes which appear under very varied circumstances may have different, but as yet unknown, life histories.

e. Basophilic Myelocytes.

f. Basophilic Polymorphonuclears: These cells again differ from the neutrophilic group in the character of their granules. Apparently two types of white cells exhibit basophilic granulation of the protoplasm. The first of these, called "Mastleucocyten" by Maximow[53], have large irregularly shaped granules which seem to be formed by breakdown of the nucleus which is usually of very irregular shape in such cells. In myelogenous leukemia it would seem probable that the increased number of mast-cells so often found is caused by an increase in the above variety. It is rare to find this type of basophil in normal blood.

The second variety of basophil is the true mast-cell. These leucocytes have fine granules like the neutrophilic series. They are formed in the bone-marrow and also in the lymph-glands and like the eosinophils are more properly tissue than blood cells. The polymorphonuclear variety is most commonly found.

The reader should understand that, while in each of the types of granular leucocytes which we have discussed the myelocyte is the youngest form and gives rise by a gradual transformation of the nucleus to the polymorphonuclear type, in all instances these cells apparently remain true to the original character of their granulation. One possible piece of evidence to make us doubt this fact may be mentioned; *i. e.* the experiments of Milroy and Malcolm[54], who found that on injection of nucleic acid the oxyphil granulations in the leucocytes of the rabbit and guinea pig become definitely basophilic. A further apparent fact relative to the granular leucocytes is that in the final age reached by these cells the polymorphous nucleus is not always found. We have frequently seen bloods in which almost all the leucocytes exhibited kidney-shaped nuclei and apparently no further stage of development could be reached.

The granular leucocytes have an inevitable association with changes in the red-cell composition of the blood. As will be seen later in our discussion of the mechanism of blood-picture formation, they tend to move with the red cells. At times this movement into the blood stream seems quite casual and due merely to the proximity of the two types of cells in the bone-marrow. In other instances there is such a definite response on the part of the leucocytes as to lead us to believe they are responding to some phase of the stimulus which is calling for new erythrocytes. The fact has been emphasized that red-cell tissue wherever found is identical. This is only true in so far as the general architecture of the tissue is concerned. It does not apply to the varieties of cells found in it. Thus red cell-forming tissue in the bone-marrow may be filled with granular leucocytic forms undergoing rapid proliferation. But in the same case this does not mean that islets of red cell-forming tissue in the liver will show just the same proportionality. Cells of both varieties are often present in such abnormal sites of blood formation but we are apt to find a specialization of effort in them.

The most conspicuous function of the granular leucocytes is phagocytosis, a property of these leucocytes rather intimately associated with their ameboid powers. Muir[55] in extensive studies of the leucocytes finds that ameboid movement begins to appear as the nucleus becomes polymorphous. Dickson[16] has seen ameboid movement in myelocytes and has observed phagocytosis by these cells. I have seen active phagocytosis by myelocytes which have been washed out of the marrow by a stream of warm physiological salt solution and kept suspended in oxygenated salt solution. There is, however, no doubt that phagocytosis and ameboid activity are much more marked in polymorphous leucocytes. Dickson[16] reports an interesting observation in this relation:

"The fresh blood from a patient suffering from myelogenous leukemia was incubated for a half-hour with living staphylococci, and many of the polymorphs were seen crowded with orangisms; in some of the intermediate cells as many as a dozen cocci might be found; while in the myelocytes proper might be seen from three to four up to six or seven at most—showing that the marrow-cells in leukemic blood are apparently capable of assuming some of the functions of the adult leucocyte, feeble, it is true, but distinctly present, the organisms being surrounded by a digestive vacuole, and in many instances being in process of disappearance by intracellular digestion. It is interesting to note that the mast-cells (basophilic granular leucocytes) which are very numerous in this specimen, and also the eosinophils, appear to take no visible part in phagocytosis, though the latter cells are, in the fresh specimens, very actively ameboid; and it is also of course possible, as has been suggested by some authors, that they may assist in the process chemically, by means of their secretions."

Kanthack and Hardy[56] found that eosinophile cells in hanging drops of frogs' lymph were attracted toward anthrax bacilli and on coming in contact with these organisms discharged their granules. Degenerative changes in the bacteria followed this discharge, presumably due to the proteolytic ferments which the granules contained.

Kite[57] has advanced observations of living leucocytes which indicate that their phagocytic powers depend to a marked degree upon sudden alterations in surface viscosity which are caused by environmental changes. In making micro-dissections of leucocytes he observed that if such a cell "is touched with a glass dissecting needle and the needle drawn away, a minute thread of hyaline cytoplasm may be seen connecting the point of the needle with the leucocyte. When motile bacteria strike this layer they stick and generally do not seem able to free themselves. The violent jerking movements made by the bacteria may serve to imbed them firmly in the surface of the leucocytes. Observations on the mesenteries of frogs, exposed to air, indicate that the well-known accumulation of leucocytes on the walls of the small blood-vessels is due, primarily, to a marked increase in viscidity of the surface layers of the leucocyte cytoplasm."

Not only do the polymorphonuclear neutrophils take up most bacteria but they apparently digest them very readily. This digestion is accomplished through the medium of proteolytic ferments[58]. In addition to protease, lipase, amylase, maltase and oxidase have been identified as endoenzymes of these cells.

In connection with the eosinophile cells it has been stated that division occurs. All of the varieties of granular leucocytes divide mitotically but division is practically confined to cells of myelocytic type. Blumenthal[59] and Renaut[60] found mitoses in neutrophilic and eosinophilic cells up to the stage of the kidney-shaped nucleus. It is probable that the leucocytes also divide amitotically, but this is apparently a rare and unimportant method of multiplication.

C. The Formation and Character of the Endothelial Leucocytes or Transitional Cells

The red blood-cells are circulating elements. Their function depends upon successful movement between the lungs and tissues. In contrast to these moving elements we have connective tissue cells which are constantly fixed in one position. Between these two types there is a large group of wandering cells found indiscriminately through the solid tissues and to a certain extent in the blood stream. The ordinary granular leucocytes are in reality such wandering elements. They are so placed as to enter the blood stream easily and represent a mobilized army ready for concentration at any point of necessity. It is probably true that they always functionate; *i.e.*, phagocytize outside the blood stream in the tissues and merely travel by the blood paths to areas of infection. In addition to the granular leucocytes there are numbers of large phagocytic cells which are usually classed as large mononuclears or transitionals when found in the blood stream. These are apparently endothelial in origin. Mallory[61] and Dickson[16] have described such cells proliferating from capillary endothelium and moving out into the surrounding tissue. In addition to endothelial phagocytes arising in this way, certain of them apparently arise from the supporting reticulum of such tissues as the marrow, spleen and lymph glands. Certain of the endothelial leucocytes may apparently be differentiated through power to take up certain dyes, such as trypan blue, vital red, etc.[62].

Whatever the final origin of the endothelial leucocytes, there can be no doubt as to their phagocytic function nor to the fact that they reach the blood stream constantly and in small numbers. Occasionally, as in cases described by Van Nuys[63], Bartlett[63], Evans[64], and Rowley[65], they were extremely numerous in the blood, but the underlying reasons for such wholesale appearance in the circulation are not known.

D. The Formation and Character of the Megacaryocytes and Blood-Platelets

Wherever red blood-forming tissue is found a definite type of giant cell, the megacaryocyte, is discoverable. In typical form these cells have a very complex but really single ring-shaped nucleus which seems to be made up of a number of large vesicular nuclei lying with edges overlapping and apparently fused together. Occasionally the typical ring or basket-shaped nucleus is not found. Instead we have a large lobulated structure of bizarre shape but again made up of what are apparently fused or overlapping nuclei. It has been held that the megacaryocytes arise from osteoblasts[66]. The view of J. H. Wright[67] that these cells arise from small mononuclear elements of distinctive type does not enable us to understand why they should become numerous where erythropoiesis is going on. Maximow[68] has shown that such cells in the rabbit arise from primitive mesameboid elements which are similar in appearance to the hemoblasts already discussed. Jordan[69] in an extensive investigation confirms this view. He believes that the megacaryocytes "represent an incidental phase of intense hemopoiesis." J. H. Wright[70] has shown that the megacaryocytes perform the extremely important function of giving rise to the blood-platelets, and his demonstration has met with ample confirmation[71]. In view of the constancy with which platelet increases in the blood stream and megacaryocyte increases in the bone-marrow accompany intensive erythropoiesis, the origin of these cells may well be referred back to the undifferentiated hemoblasts.

Megacaryocytes and blood-platelets are ameboid[72]. The former have been pictured[16] as containing leucocytes. Jordan[69], however, believes them to have no phagocytic function and thinks that leucocytic inclusions more probably mean invasion of degenerating giant cells. The megacaryocytes are usually placed very near, often surrounding capillaries. Into these their ameboid cytoplasm finds its way and eventually breaks up into clumps of platelets which circulate freely and are also ameboid[72]. The platelets are the principle source of prothrombin[14], an indispensable factor in blood coagulation, and also furnish a certain amount of thromboplastin or thrombokinase, another factor in the same process. In the study of blood diseases, owing to the fact that platelet formation incident upon megacaryocyte proliferation[73] precedes or accompanies erythropoiesis, and owing to the readiness with which the platelets may be counted in the circulating blood[74], we have in them a valuable index of the condition of the blood-forming tissues.

The proximity of the megacaryocytes to the capillaries leads one to suspect that they may occasionally be found in the circulating blood. Fair-sized fragments are often seen and whole cells frequently break loose, but in such case, due to their great size, are filtered out in the lung capillaries and are rarely discovered in blood smears[75]. The finding of definite megacaryocytic fragments indicates marrow disintegration rather than favorable proliferation.

An interesting point relative to platelet morphology is the great difference in size which these elements may show. In normal blood they are smaller than erythrocytes and show no evidence of nucleus formation. At other times they may be larger than the erythrocytes and may show grouping of granular material into conventional nuclear shape. As yet, no systematic observations exist upon the significance of form variations or granularity of platelets. Finally, Fonio[76] and Minot and Lee[77] have shown that the platelets in hemophilia, while in no way different in appearance or number, differ qualitatively in their unreadiness to break down and give up the prothrombin which originates in them.

E. The Formation and Character of the Lymphocytes

Just as in the case of the granular leucocytes, the adult typical lymphocytes are easy to identify. They arise in lymphadenoid tissue wherever it is found, in the lymph-glands, the spleen, the thymus, etc. Lymphocytes vary in size and with this variation bring us face to face with the old problem of the kind of cells finally responsible for them. It is easy to account for the lymphocytes of the normal blood smear in terms of the small elements found in the periphery of the germinal centers in the lymphadenoid organs. But when one is faced by the origin of foci of lymphoid tissue all over the body, as in lymphatic leukemia, and finds cells in the circulation, which are as large or larger than many polymorphonuclear leucocytes, possessing a moderate amount of basophilic non-granular cytoplasm and a loosely reticular, lightly staining, nucleus, one is forced to consider what cells give ultimate origin to the lymphocytes. As in the case of the granular leucocytes, such forms as have just been mentioned are identified through the company they keep and not through their individual characteristics. The erythrocytes, the granular leucocytes and the megacaryocytes have already been referred back to an undifferentiated hemoblast, and the lymphocyte must now be added to the genetic possibilities of these cells. It should however, be emphasized that this does not mean absolute identity in the origin of these cells which differ so markedly in their adult condition. It simply means that, with the present powers for identification, a cell is finally reached which cannot be placed with certainty by any chemical or morphological methods now available. Staining reactions[78] designed to show granulation in white cells, which with the ordinary stains, such as Wright's, are non-granular, are useful but fail to reach back far enough.

Van der Stricht[79] and Kostanecki[80] first pictured the origin of the lymphocyte from the primitive hemoblasts. Flemming[81] showed that they multiply by mitotic division in the lymph-glands, but the question how the original cells of origin get into the lymph-glands is unanswered. The normal lymphocyte is almost exactly the same size as the red blood-cell. It possesses a round or slightly indented nucleus nearly filling the cell and dense in character. Both nucleus and the narrow regular rim of cytoplasm are basophilic. The small lymphocytes are slightly ameboid and the larger forms quite actively so[82]. In no case, however, can definite lymphocytes be shown to be phagocytic. They are widely distributed throughout normal tissues and gather in great numbers about chronic foci of damage. Murphy[83] in a series of papers has shown that the lymphocytes are the chief agents in the destruction of tissue grafts in animals. His work also indicates that the lymphocyte, which becomes so numerous about tuberculous foci, is an important agent in controlling the process. How the lymphocyte actually achieves this result is unknown. These views of the function of the lymphocyte are made more forcible through the facts that, in fatal acute miliary tuberculosis, the lymphocytes in the blood stream fall from their normal percentage of 20 to 10 and that in cases of healing tuberculosis they may often form 50 per cent. of the total leucocytes[84]. Lymphocytes have been shown to possess a proteolytic ferment[85].

A tabular summary of the blood-cells can now be constructed in accordance with our statements as to the origin of the difficult elements. (Fig. 1.) It should, however, be understood that the final steps in the life history of the blood-cells have not as yet been taken and that the table presented merely indicates what is considered the best view of a confusing situation.

BLOOD FORMATION

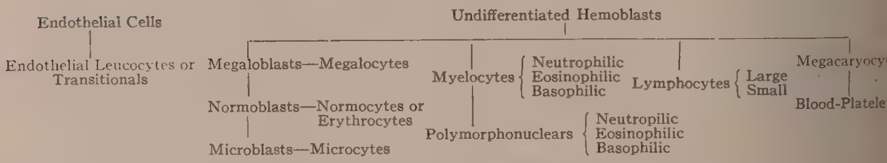


Fig. 1.—Tabular summary showing probable origin of blood cells.

THE PASSAGE OF BLOOD-CELLS FROM THE MARROW TISSUE INTO THE BLOOD STREAM

A. *Passage into the Blood Stream of the Erythrocytes*

Our discussion to this point has resulted in a listing of the different blood-cells, together with a description of such peculiarities as may best seem to identify them both in the blood-forming tissue and in the blood stream. Aside from brief mention of the vascular conditions in the marrow, the fundamental problem of the delivery of the blood-cells into the circulation with the resulting formation of what we call the normal blood picture has not been considered. It is our purpose in this section to discuss the actual delivery of cells, and in following sections, the character of the stimuli inducing delivery.

Owing to the facts that bone-marrow is widely distributed in the body and that it is encased in such a way as to render it peculiarly inaccessible, very little attention has been given to the actual manner in which the tissue delivers its product to the blood stream. In glands such as the liver we trace the bile in orderly passage from the liver-cells to the duodenum. In other instances, such as the pituitary gland, we are in doubt as to the method of delivery of the secretion. It reaches the blood stream, but just how we cannot say. The bone-marrow consists of a tissue which secretes cells into the blood stream, and this secretion is accomplished in the constant and economical manner befitting a function of such extreme importance. The result of this process is the normal blood picture, and we may well ask what is known as to the details of its formation. The reason why the cavities of bones have been made the seat of normal blood formation has never been given, and it should be understood that the statements which follow are not advanced as reasons for blood formation inside bones, but simply bring out the extreme advantage of formation in this position.

In discussing the marrow architecture we commented upon the controversy which has surrounded the character of the marrow capillaries, and said that these vessels, while at times open structures communicating freely with the marrow reticulum, tend always toward closure and in the adult mammal are probably always closed. MacCallum[86], in dealing with this question remarks, "The capillaries are wide and variable in diameter, and it is frequently difficult to trace their endothelial outlines. Indeed, one does not receive the impression that they are stout-walled tubes capable of carrying blood safely at a considerable pressure, but rather that their walls are extremely thin if not actually lacking in places. At times it seems as though the mass of cells in the reticulum were continuous with those within the capillaries, and one must suppose that some such relation may exist, to explain the phenomenally rapid delivery of cells into the blood-stream." We have already said that blood-forming tissue wherever found has the same character, a loose reticulum carrying the blood-forming cells, and pierced by capillaries of extreme tenuity of wall. The enormous advantage which a bony case gives such tissue is at once apparent. Even though the capillaries are extremely thin, their walls are as strong as the compact bone which ultimately encloses them and from which they are separated by the incompressible semi-fluid marrow tissue.

If we ask ourselves why it is that cells such as nucleated red elements and myelocytes, normal to the marrow but abnormal when found in the blood stream, are not always flooding out into the peripheral blood, we are at a loss for an answer until we recollect conditions imposed by the position of the blood-forming tissue in the adult. It is essential that new erythrocytes be delivered steadily into the circulation and it is improbable that this delivery depends upon movements of the cells themselves. Ameboid activity has been observed by Emmel[27] in the nucleated red cells of pigs' blood, and by Morris and Thayer[87] and Thayer[88] in human blood. It is not hard to see traces of ameboid movement in human blood when one has preparations filled with large cells. These will show it in their non-nucleated condition but never vigorously, and it is in no way probable that ameboid activity has anything to do with the movement of red cells into the blood stream. They do not migrate as do the granular leucocytes, endothelial cells, and blood-platelets. Kite[57] has shown that under dark field illumination and proper conditions the erythrocytes extend fine flagellar processes which may be retracted very rapidly and which may move so vigorously as to cause a feeble but definite swimming of the individual cell. Just how far such movement can aid in the extension of cells, it is not possible to state. We are inclined to believe it of very little importance. The red cells are delivered as a result of growth in an inexpansible environment. It is our view that the movement of red cells into the circulation is directed by the stimulus resulting in their formation. Bunting[89] and Selling[90] have brought out the fact that the erythrocytes grow in definite groups or colonies in the bone-marrow, nucleated elements being the rule in the center of these colonies with cells toward the periphery becoming progressively more adult. In normal red marrow, the packing with cells engaged in red and white cell formation more often than not makes it impossible to get a clear impression of this colony type of structure. In regenerating red marrow, colonies may often be seen very well. The normal adult, whose blood picture is remaining quite constant from day to day as a result of steady delivery of erythrocytes to make up for their equally constant destruction, is experiencing the inevitable result of growth in a closed space. As proliferation in these erythrogenetic centers occurs either more room must be made in the marrow cavity for the cells formed or else they must be forced into the circulation. The marrow capillaries contain blood at a very low pressure and it is into these yielding structures that growth steadily forces adult red cells.

Obviously, from such a view, the character of the blood picture depends not upon the amount of blood-forming tissue which may be found at autopsy in the marrow cavities, but entirely upon the rate at which this tissue is growing. Under ordinary circumstances the shaft of the long bones is filled with fat, and formative marrow is not found until we almost reach the extremities. But fat, enclosed in a bony case, serves just as well to direct the operation of growth pressure toward the capillaries as would solid bone. Pathologists have often been surprised because cases showing the blood picture of aplastic anemia have had red marrow in their bones and sometimes plenty of it. Red marrow as we view the problem can make no impression on the composition of the circulating blood unless it is growing. The moment growth stops or ceases to be active enough to force more than a minimal number of red cells into the circulation, the tissue is of no functional use. Usually when marrow growth stops there is a fairly rapid appearance of aplasia and no formative marrow is found at autopsy. We believe, however, that instances of arrest, or rather extreme sluggishness, occur in which even a considerable quantity of red marrow may be found after death. In such instances the judgment of the pathologist as to the diagnosis of aplastic anemia should be based upon evidences of division in the marrow-cells, and if there is no sign of proliferation he may explain the apparent aplasia as judged from the blood findings as a result of arrested growth.

It is clear that blood-forming tissue is peculiarly adapted to serve just such a method of secretion as we have described. The delicate capillary walls oppose no resistance to the slight but insistent drive of growth pressure. At the same time these walls serve to direct the blood current and, under the extreme vicissitudes of blood flow to which mammalian bone-marrow is subjected, protect the tissue in the sense of preventing an indiscriminate washing out of immature cells.

In the light of the above considerations, let us follow the changes occurring in the bone-marrow together with their effects upon the blood picture following a series of hemorrhages. The loss of blood at once upsets the balance between cell formation and cell destruction. The organism experiences a red-cell content intolerable to it and blood formation at once increases. It is possible that speeding of formation by the tissue in existence at the time tends at first to meet the emergency, but as soon as possible extension of red cell-forming tissue takes place. Keeping pace with this growth, fat and bone are rapidly absorbed, but the stimulus for blood formation must operate with extreme slowness in order to prevent overfilling of available space and consequent forcing of nucleated red cells into the circulation.

The appearance of normoblasts in the circulation after one large hemorrhage is thus evidence of overcrowding. It is upon examining such marrows as these that one is apt to come to the conclusion that blood channels and marrow parenchyma are quite continuous. There is no doubt that this is frequently true, but as the processes incident upon marrow growth continue, more room is made for the blood-forming cells, and the normal orderly arrangement of the marrow is again found with nucleated red cells out of the active blood current and free from the danger of being swept into the blood stream. In a long series of observations designed to test the integrity of the marrow tissue when assailed by varying types of mechanical strain[13], it has been found that the amount of tissue is not the factor controlling delivery of red cells. The blood flow through marrow tissue may be increased to many times the normal rate without dislocating nucleated red cells unless the tissue at the moment of the experiment is itself in such condition as to force nucleated elements into the blood stream.

From the view of red-cell extrusion which we have advanced, it follows necessarily that any process of growth in the marrow may serve to drive nucleated red cells into the circulating blood. Ewing[91], Reider[92], and Sherrington[93] have noticed nucleated red cells in the blood as a result of leucocytic proliferation. Mere migration of leucocytes does not, however, cause nucleated red-cell dislocation. It has been emphasized[13] that post-hemorrhagic leucocytosis is one of the most constant findings immediately following hemorrhage. But normoblasts appear in the blood stream several days later. The immediate leucocytosis after hemorrhage is not a result of proliferation but of mobilization of cells already in existence. It is peculiarly true in children, where there is a large volume of red marrow, that rapidly occurring leucocytosis as in pneumonia is frequently accompanied by the finding of nucleated red cells in the blood stream, and we may look upon these cells as pushed out by the rapidly developing leucocytes. A similar forcing out is often seen in leukemia and in bone-marrow tumors.

If mammals are bled repeatedly, the blood being taken just as rapidly as the blood picture returns to normal, it has been shown, in the first place, that the blood-forming tissue does not become exhausted[94]. It is impossible to produce aplasia in this way. What is significant is that after a time normoblast extrusion is not seen. The accompanying chart (Fig. 2) shows this fact very well and illustrates other points relative to red-cell delivery, namely, the tendency of nucleated red cells to reach the blood stream in "crises" or spurts. Such "crises" were first noticed by von Noorden[95]. They are the natural result of the fact that increases of erythrocyte count in the blood following hemorrhage are step-like in character and do not give the smooth curve which would characterize a steady process.

There are several points in relation to the extrusion of red cells and their appearance in the circulation which are not well understood. The first of these is the possible influence on the blood picture of red-cell formation in the spleen and liver as a result of prolonged stimulation of production. We have said that red blood-cell forming tissue is the same wherever found and we have also advanced reasons for believing that such tissue can exist most successfully in a bony case. So far as we know there are no careful efforts to estimate the effects on the blood picture brought

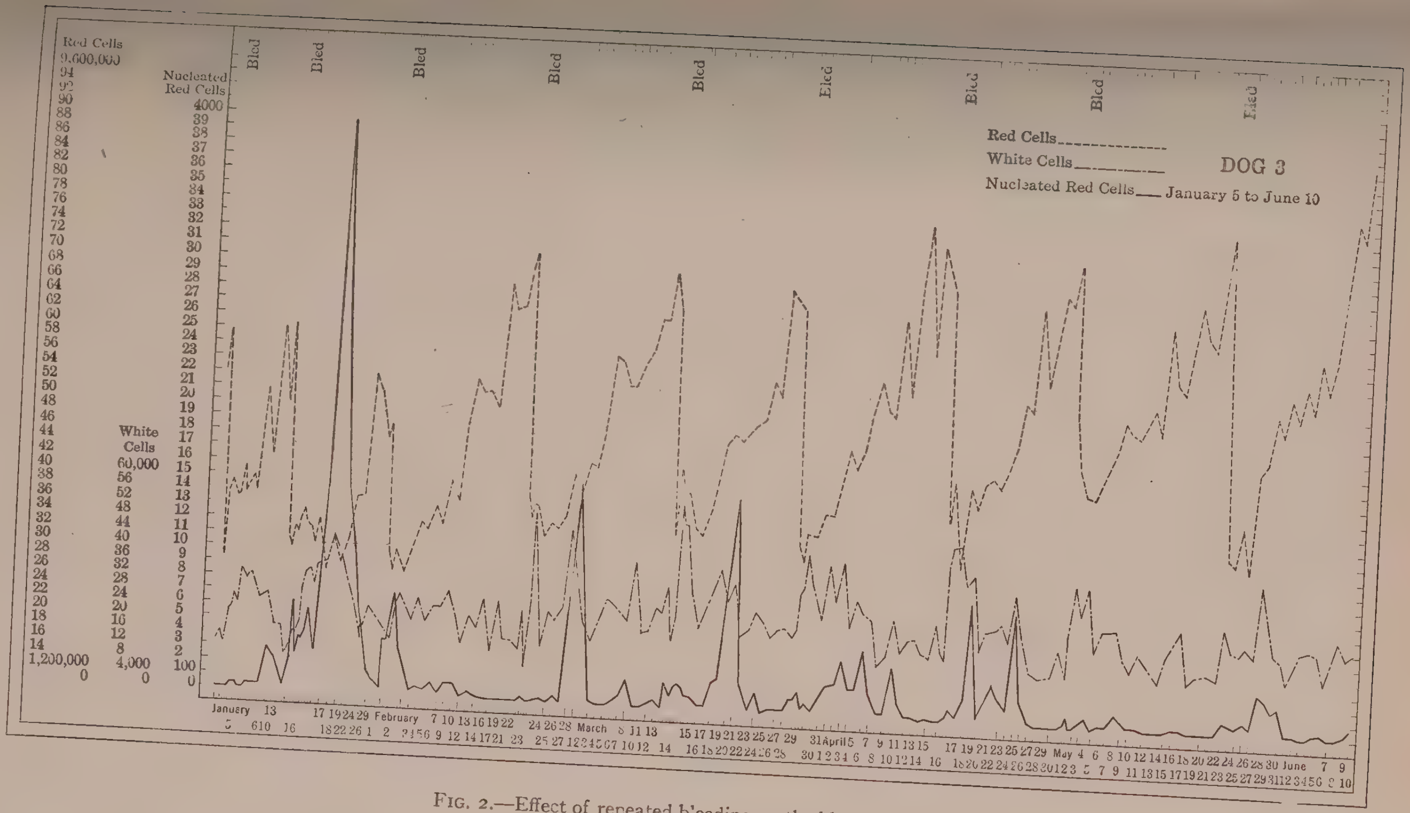


FIG. 2.—Effect of repeated bleeding on the blood-cells.

about by the presence of blood-forming tissue in the liver and spleen. Whether red cells, nucleated or non-nucleated, leave these sites more readily than the bone-marrow is not as yet even subject for speculation. Morris[96] has compared the composition of splenic vein blood with that of the splenic artery. He reports an increased number and "more perfect and larger red corpuscles than that of the artery and they seem richer in hemoglobin." Krumbhaar and Musser[97], publishing at practically the same time, find no differences whatsoever and their conclusions are based upon a better conception of the possible errors in blood counting. Secondly, and a matter of great interest, is the possible effect of the spleen aside from the question of being a site for red-cell formation. Minot and Lee[37], following Naegeli[18], suggest that the numerous blasts and cells containing Howell-Jolly bodies which are found after splenectomy in man indicate that removal of this organ lowers the threshold for extrusion of red cells by the bone-marrow. Pearce and his co-workers[33] have summarized the literature upon the relation of the spleen to blood formation and destruction. One cannot but feel on going over their experiments and those of others in the field that astonishingly few positive facts can be listed as functions of the spleen. Following extirpation of the normal spleen in animals and of the normal spleen in man, a moderate secondary anemia occurs and there is a tendency toward increase of young forms in the blood stream. Much later the animal may exhibit a definite polycythemia. The anemia is less marked when the spleen is the possible site of disease as in certain cases of pernicious anemia, hemolytic jaundice and Banti's disease. This discrepancy is possibly an unreal one and is based upon the fact of different degree of activity in the marrow at the time of splenectomy. If the spleen is removed in the presence of a large volume of red marrow there is a supply of young cells, easily recognizable when extruded, whereas with a normal marrow such cells are less numerous and less strongly pressed toward the blood stream. Experimental splenectomies at varying periods after hemorrhage in animals would do much to clarify this point, but such experiments do not exist. Indeed, in most of the experimental work upon anemia, there has been a lack of attention to the possible amount and condition of the blood-forming tissue at the time hemorrhage, splenectomy, or other experimental manoeuvre was instituted.

B. Passage into the Blood Stream of the Granular Leucocytes

These cells are ameboid and pass readily into the blood stream by virtue of this activity. If formation is very rapid, more so than space permits, they also are driven into the circulating blood by growth pressure. In the section upon leucocytosis and leucopenia the conditions bringing about growth and disappearance of the bone-marrow white cells will be considered.

The actual movement of these cells from the marrow into the blood stream needs no further discussion.

C. Passage into the Blood Stream of the Endothelial Leucocytes

These apparently reach the blood stream as a result of their ameboid activity.

D. Passage into the Blood Stream of the Megacaryocytes and Blood-Platelets

In the section on "The Formation and Character of the Megacaryocytes and Blood-Platelets" (*cf.* p.526) we have discussed the relation of the megacaryocytes to the blood-vessels and the manner of origin of the blood-platelets. Apparently the number of these latter elements in the circulating blood depends upon the number of megacaryocytes in the organism and their activity in forcing their own cytoplasm into the capillaries. Ameboid movement is probably in the main responsible but pressure from active marrow growth may also play a part.

E. Passage into the Blood Stream of the Lymphocytes

These cells are formed in a variety of positions and probably take different paths to the blood stream. In the cortical substance of the lymph-nodes there is a dense packing of lymphocytes which are, however, disposed systematically. Numerous germ centers occur filled with large actively-dividing cells. On the periphery of such centers smaller forms, corresponding to those seen in the blood, are found. As growth goes on, the adult lymphocytes are forced toward the lymph sinuses which surround the cortical substance and are then slowly carried off by the lymph stream. Ehrlich[98] believes that absolute lymphocytosis depends upon production of lymphocytes in the lymphoid tissues but also upon flushing out of these tissues by increased lymph flow. So far as we know direct observations upon the numbers of lymphocytes in the lymph stream leading to and away from single lymph-glands do not exist. Owing to the fact that the thoracic duct forms the final path for delivery of most of the body lymph to the blood, numerous studies have been made upon the cells in this lymph. Rous[99] has found that factors increasing the flow of thoracic duct lymph increase the number of lymphocytes found in it. Different methods of increasing lymph flow were used, such as muscular activity, intravenous glucose injections, and pilocarpin.

There is no doubt that many lymphocytes are furnished to the blood stream by the lymphatic path. The fall in the blood lymphocyte content following the ligation of the thoracic duct and the excision of large bodies of lymph-glands testify to this[100]. While it is probable that the ordinary encapsulated lymph-glands furnish few lymphocytes to the blood by direct movement into the small blood capillaries traversing them, it is impossible to view conditions in the spleen without the belief that lymphocytes may readily gain direct access to the blood stream in this organ. There is, however, no direct evidence for this belief. The circulation through the spleen is an open one[101]. Blood undoubtedly moves slowly through the splenic pulp where it has opportunity both to lose and to collect cells. Mall[101] has shown that the movement of cells out of the splenic pulp is due to the muscular contractions of which the organ is capable. Owing to the fact that the flow of blood through the spleen is rapid and large we must realize that studies of the composition of splenic artery and splenic vein blood are singularly unlikely to differ, and we have already mentioned direct evidence to show that they do not within our powers of estimating differences. It is obvious that in the spleen, by virtue of the smooth muscle in the capsule and trabeculae, we have an active arrangement for emptying the organ. In the bone-marrow, pressure for cell delivery is obtained through growth in an inexpansible space. Harvey[102] has shown that in certain of the lymph-nodes smooth muscle contractions may aid in squeezing out the cells. In others where there is little or no capsule, movement out with the efferent lymph must be a very casual matter. Splenectomy is sometimes followed by a lymphocytosis which is slow in development and of unknown cause.

The Normal Blood Picture

From sea-level to an altitude of one thousand feet the erythrocytes in man (adult) vary between 4,000,000 and 6,000,000 per cubic millimeter. It has been held that 5,500,000 is the upper limit for women, but 500,000 more cells may be found without evidence of any abnormality. In making red-cell counts the operator must be sure that the capillary blood he is studying is flowing freely. Red cells tend to sediment in the vessels and in order to have an accurate picture of the concentration of cells really in the blood current one must be sure of active flow. Under ordinary circumstances red-cell enumerations from venous blood will be more constant than those from capillary blood. This difference ceases to exist if moderate exercise precedes withdrawal of the capillary blood, the exercise insuring active movement of all the red cells and uniform concentration through the mixing which occurs. Modern methods for the determination of hemoglobin aim toward a degree of accuracy which has heretofore been conspicuously lacking in clinical estimations of this substance. Palmer[103] gives the following directions for hemoglobin determination.

Palmer's Method of Hemoglobin Determination

"Blood is obtained in the usual manner by pricking the finger or lobe of the ear. A 1 per cent. solution of blood is made by drawing 0.05 c.c. into a special pipette and transferring into 5 c.c. of 0.4 per cent. ammonia solution—accurately measured with a calibrated pipette or burette into a 12 x 120 mm. test-tube.' The blood pipette is rinsed out by drawing into it two or three times the ammonia solution. Ordinary illuminating gas is bubbled rapidly through the ammonia blood solution for 30 seconds, after which, it is compared in a Duboscq colorimeter with a standard carbon monoxide hemoglobin solution set at 10. The average of at least four readings is taken. The calculation is simple, $\frac{10}{R} \times 100 =$ per cent. hemoglobin.

"*Manner of Obtaining Blood.*—With sufficient care the usual clinical method for obtaining small amounts of blood by pricking the ear or finger is satisfactory. A free flow is essential. Any undue manipulation or squeezing of the part should be avoided because an error of 5 or 10 per cent. may be introduced by diluting the blood with tissue juice. Where there is marked anemia requiring larger amounts of blood than 0.05 c.c., or where there is difficulty in obtaining blood from the ear or finger, venous puncture should be used, coagulation being prevented with oxalate or citrate salts. It is often practical and convenient to combine the determinations of hemoglobin with other blood analyses, where venous puncture is required. If blood has been drawn by venous puncture care must be taken that the corpuscles and serum are well mixed before filling the pipette. The blood should never be shaken violently before measuring, because it becomes filled with air bubbles. The mixture of corpuscles and serum may best be accomplished by first giving the receptacle a circular motion and finally stirring briskly with a glass rod or measuring pipette which is filled while stirring the blood.

"*Pipette for Measuring Blood.*—The pipettes are made of millimeter glass tubing calibrated to contain 0.05 c.c. and 0.1 c.c. The pipettes are easily made in any laboratory from straight tubing, and require no blowing, the point being rounded off on an emery wheel. In this way time and expense are saved, since pipettes obtained from glass blowers require recalibration before use. It has been found that water may be used for this calibration, as pipettes which have been calibrated with mercury and water check sufficiently well. The advantage of having the pipette calibrated to contain 0.1 c.c. as well as 0.05 c.c. is obvious. In bloods with a low hemoglobin content, 0.05 cc. may not be sufficient to give color necessary for accurate color comparison in the colorimeter. A pipette of this type, and used in the manner described, is capable of measuring 0.05 c.c. of blood with an accuracy of 0.2 per cent.

"*Ammonia Solution.*—Ammonia solutions, containing 4 c.c. of strong ammonia in 1 liter of water, suggested by Krogh, are used, because the full color of the carbon monoxide hemoglobin develops at once.

"*Saturation with Carbon Monoxide.*—Ordinary illuminating gas as a source of carbon monoxide has proven entirely satisfactory. It was thought that there might be substances other than carbon monoxide in the gas which might form hemoglobin compounds and interfere with the determination. Accordingly, pure carbon monoxide was prepared by heating oxalic acid with concentrated sulphuric acid and passing the gas produced through sodium hydroxide to free it from carbon dioxide. As far as could be determined on comparison of the two solutions in the colorimeter, the colors were identical. Oxyhemoglobin solutions are very unstable. Hence it is necessary, after transferring the blood to the ammonia solution, to saturate with carbon monoxide within an hour. After saturation with carbon monoxide, the solution may, on carefully stoppering and protecting from light, be placed in the ice box and the determination made at leisure. Saturation of the blood should be carried out under a hood. If the laboratory does not possess a hood, the saturation may be accomplished under a funnel, attached to a small water vacuum pump, to remove the gas.

"*Standard Hemoglobin Solution.*—Haldane's standard of a 1 per cent. solution of a blood having an oxygen capacity of 18.5 per cent. is used. It has been shown by Haldane and Smith[104], Butterfield[105], Barcroft[123], and others, that the oxygen capacity of the blood depends upon its hemoglobin content. A blood of 18.5 per cent. oxygen capacity contains approximately 14 gm. hemoglobin per 100 c.c. Although the blood of normal men in this country, as shown by Meyer and Butterfield[106], Williamson[107], and also as we have found by use of the method here described, contains on the average 16.6 gm. of hemoglobin, which would correspond to an oxygen capacity of about 22 per cent., it was thought best to keep Haldane's standard for the present. It is a simple matter to compute the grams of hemoglobin in any given blood from the results obtained.

"The standard hemoglobin solution is prepared as follows: A quantity of defibrinated human or ox blood is obtained. The oxygen capacity is determined by the method of Van Slyke[108]. The blood may also be standardized by a spectrophotometer or solutions made from hemoglobin crystals prepared in the manner described by Butterfield[105]. We have checked several times our standard and found that the oxygen capacity method for standardization is most convenient and satisfactory. The blood is diluted with 0.4 per cent. ammonia solution so as to make a 20 per cent. solution of a blood with an oxygen capacity of 18.5 per cent. This 20 per cent. blood solution is then saturated with carbon monoxide by bubbling through it illuminating gas for 10 minutes. A drop of caprylic alcohol prevents troublesome foaming. The glass tube through which the gas is passed into the blood solution is withdrawn slowly and the bottle stoppered immediately. Rubber stoppers must not be used in connection with hemoglobin solutions. The cork should be sealed in with paraffin and the solution, protected from light, kept in the ice chest. Such a solution thus protected will keep for months. Several solutions now nearly a year old prepared in this manner have shown no deterioration. 5 c.c. of this 20 per cent. blood solution made up to 100 c. c. with 0.4 c.c. of ammonia solution and saturated with carbon monoxide, make the 1 per cent. standard for use in the colorimeter and may be prepared from time to time as desired. The 1 per cent. standard for routine use may be kept in a dark glass or black painted aspirator bottle, the lower opening of which is provided with a cork, through which passes a glass tube with a ground glass cock for withdrawing small amounts of solution. A glass tube is put through the cork in the top of the bottle and extends to the bottom. Both corks should be sealed with paraffin. This glass tube is connected with an open gas fixture in order that when solution is withdrawn from the bottom, gas rather than air will enter to replace it. Solutions thus prepared may keep for several weeks; but, as a precaution, it is advisable to make fresh 1 per cent. solutions frequently; *i.e.*, every two or three weeks. It should be remembered that dilute hemoglobin solutions are less stable than concentrated solutions; and that hemoglobin solutions keep best in the cold and protected from light. The first indication of solution deterioration is a change in color from the characteristic cherry-red of carbon monoxide hemoglobin to a red with a brownish tinge, due to the formation of methemoglobin.

"*Comparison in Colorimeters.*—The Duboscq or Kober colorimeters have proven to be by far the most accurate and satisfactory instruments for this colorimetric work. Other colorimeters, however, may be used. The difficulties encountered are those inherent in all colorimetric work and in this connection reference to Kober's[109] article may be made. The color of the carbon monoxide hemoglobin, because of the relatively low stimulus threshold for the eye, is admirably suited to colorimeter comparison, slight differences being easily detected. We prefer to use the daylight from a north window. Satisfactory results are, however, obtainable with artificial light when "daylight glass" is used between the source of light and the solution. Considerable experimentation with light filters has failed to improve on the accuracy with which the comparison may be made. No difficulty should be experienced in making the readings check within 0.2 of a single division on the colorimeter scale.

"Color comparisons are most accurate when the unknown hemoglobin solution reading falls between 9 and 11 on the colorimeter scale. If the reading of the unknown falls below 8 or above 12, another sample should be taken and the dilution made such that the reading will fall within these limits. This is easily accomplished by varying the amounts of blood and ammonia solution, making the necessary correction in the colorimeter. 2 c.c. of solution is adequate for the Kober instrument and 5 c. c. for the Duboscq. If a Duboscq or a Kober colorimeter is not available, the Hellige instrument may be used. The 1 per cent. hemoglobin standard may be sealed with paraffin into the wedge and the wedge, when not in use, kept in the ice box and protected from light. Attention should be called to the fact that the scales of the Hellige colorimeter are often inaccurately placed. The standard solution must be checked against itself and the scale adjusted so as to read 100 when the color in the cup and wedge match. We have found more difficulty in obtaining accurate checks with this instrument than with the Duboscq or Kober colorimeters; but with care the error should not exceed 2 per cent. Two c.c. of solution are sufficient for the Hellig cup, hence the Sahli pipette, which contains 0.02 c.c. of blood, may be used with this colorimeter. As large errors have been found in the calibration of the Sahli pipettes, it is necessary to recalibrate them before using."

The white cells in adults number from 6,000 to 10,000 per cubic millimeter, and again the enumerator must assure himself that in so far as is possible the blood withdrawn really represents the concentration throughout the body. Extreme vasoconstriction such as occurs immediately after a large hemorrhage may filter out many leucocytes before the capillaries are reached.

According to Miller[110], the percentages of the white cells may be tabulated as follows (Fig. 3):

P. M. N.		P. M. E.		P. M. B.		S. M.		L. M.		T.	
Percentage Values	No. of Counts	Percentage Values	No of Counts	Percentage Values	No. of Counts	Percentage Values	No. of Counts	Percentage Values	No. of Counts	Percentage Values	No. of Counts
Over 80%	4	Over 5%	74	Over 1%	137	Over 37%	57	Over 15%	18	Over 4%	79
70–80%	135	4–5%	65	0.4–1%	351	25–30%	124	10–15%	101	2–4%	418
60–70%	362	3–4%	72	......	162	20–25%	243	5–10%	359	0–2%	153
50–60%	126	2–3%	207	......	...	10–20%	219	Under 5%	172	.....	...
40–50%	21	1–2%	125	......	...	Under 10%	7	....	...	.....	...
Under 40%	2	Under 1%	107	.....	...	....	...	....	...	.....	...
Total	650		650		650		650		650		650

Fig. 3.—The group distribution of 650 differential counts made on 230 normal individuals.*

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* This table is copied from the Johns Hopkins Hospital Bulletin, 1914, X, 320.

1. "The total leucocyte count and differential formula in normal individuals are subject to relatively wide variations, which must be considered in the interpretation of studies made upon the bloods of individuals presumably suffering from abnormal conditions.

2. "The interpretation of any differential count should be based upon:

   a. "A knowledge of that particular individual's normal blood picture, when possible.

   b. "The average values for the locality in which that individual resides.

   c. "A consideration of those factors peculiar to the individual which might modify that particular blood.

3. "Differential leucocyte counts should always be reported in terms both of percentage and absolute numbers per cubic millimeter, and in all cases, where possible, more than one differential count should be made, especially in borderline cases in which slight changes are to be regarded as of diagnostic or prognostic value.

4. "The tendency to ascribe a diagnostic value to lymphocytosis is probably overdone. Only when the mononuclear elements constantly exceed the average percentage, absolute values and upper limits of variation (35 to 40 per cent.) for the community and when all modifying factors are considered, should one attempt to draw valuable conclusions from the figures obtained."

The blood-platelets commonly vary between 200,000 and 600,000 per cubic millimeter. The age of the individual causes the red-cell and platelet counts to vary towards the high normal level in infancy and childhood and to swing toward the low normal level after the fiftieth year. The white cells tend toward slightly higher numbers in infancy and youth—excluding from consideration the leucocytosis occurring at birth which is apparently a reactive phenomenon—but differ much more markedly in kind. The polymorphonuclear neutrophils make up 18 to 40 per cent, of the white cells of the child and small lymphocytes 35 to 60 per cent.

Both research and practice have tended to consider concentration of blood-cells per cubic millimeter as representing the total amount of blood in the body. While it is probably true that the normal healthy adult keeps a remarkably even volume of fluid the possibilities for variation in the various blood diseases are not as yet known.*

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* For details relative to methods of determining blood volume and the possible variations under pathological conditions, readers are referred to the following papers:

1. Keith, N. M., Rowntree, L. G., and Geraghty, J. T.: *Arch. Int. Med.*, 1915, XVI, 547.
2. Robertson, O. H., and Bock, A. V.: *Jour. Exp. Med.*, 1919, XXIX, 139 and 155.

ALTERATIONS IN THE BLOOD PICTURE UNATTENDED BY BLOOD FORMATION

A. Acute Polycythemia

Lamson[111] has shown that large injections of adrenin in animals will cause a rapid increase in the number of circulating red cells. This reaction occurs rapidly, being quite definite in ten minutes, remaining for about thirty minutes after the injection, and then slowly returning to normal. This polycythemia is in no way due to formation of new cells but in some manner not thoroughly understood is brought about by the liver, the probability being that red cells lying normally in the enormous capillary bed of the liver are thrown suddenly into the circulation. Loss of fluid from the vessels accompanies the reaction and assists in the blood-cell concentration. Lamson[111] has also shown that a similar acute polycythemia attends emotional outbursts, and this again may be referred to the adrenin discharge accompanying such states.

What is probably the same type of rapidly occurring polycythemia occurs on first passing from a low to a high altitude. It is often noted that an increase in red blood-cell count of several hundred thousand takes place on first making such a change, but the final increase of red cells representing the normal of the individual for the altitude in question is delayed for several months[112]. In such case, we must assume that the decreased oxygen supply of the high altitude results in an immediate movement in the circulation of all the red cells in existence. The new blood counts simply record the true vascular content of cells. Schneider and Havens[113] showed that the ordinary slight increase in circulating red corpuscles brought about by hard exercise, and correctly attributed by Hawk[114] to sudden passage into the moving blood stream of cells lying dormant in areas of sluggish blood current, was absent when exercise was taken at high altitude. Such individuals have simply given up their reserve. It is probable that a similar condition would be found to exist after moderate hemorrhage, individuals losing from 300 to 500 c.c. of blood giving up their normal reserve but not encroaching on the number of erythrocytes which suffices for resting conditions. If this question of red-cell reserve is appreciated the observer will not be disturbed by occasional rapid changes in the red-cell count which are in no way related to cell formation.

A final type of acute increase in erythrocyte count is seen in sudden non-fatal obstructions of the pulmonary circulation. In such cases there is a prompt stuffing of the capillaries with blood and a moderate increase in concentration.

B. The Physiological Leucocytoses

Strictly speaking all leucocytoses are physiological in that they express a normal reaction against toxic onslaught. Custom has, however, included under the term "physiological" certain minor changes in the white-cell count which are unattended by immediate proliferative activity in the leucocyte-forming bone-marrow. In *infancy*[115], for the first two to four days, there is usually a true polymorphonuclear leucocytosis with a count of 12,000 to 35,000 per cubic millimeter. As time passes, this count tends to fall to the neighborhood of 11,000 and the percentage of polymorphonuclear cells drops while the lymphocytes increase until they make from 40 to 60 per cent. of the white cells found. This last condition usually holds for the first two years of life when the normal adult percentages slowly begin to be established. There is no adequate explanation for the polymorphonuclear leucocytosis at birth.

Digestion[116]—Apparently digestion of protein alone causes a leucocytosis reaching its height about three hours after eating. The number of cells rarely goes above 15,000 per cubic millimeter, and while the polymorphonuclear leucocytes increase, most of the change is upon the lymphocytic side. Were it not for the fact that fatty meals, provocative of a maximum lymph flow, are comparatively ineffectual in causing this change when compared with a meal of solid protein material, we should be inclined to ascribe it to simply washing out of the abdominal lymphatics. Downs and Eddy[117] in a series of papers have attempted to attribute the leucocytosis of digestion to the presence of pancreatic secretin in the blood stream, but the possibility of other protein substances in the blood stream at the same time makes it impossible to attribute the condition to this substance alone. Goodall, Gulland and Paton[116] believe the source of the leucocytes in this leucocytosis to be the bone-marrow and offer evidence that the white cells in the marrow divide actively during digestion, but such observations are extremely hard to control and can be given no final credence. In the earlier days of hematology the absence of digestive leucocytosis was advanced as a possible point in the diagnosis of gastric carcinoma. While this is probably true in very advanced cases, in which it is usually quite unnecessary to apply such a test, it is quite unreliable in early states where diagnosis is most important[118].

Vigorous *exercise*[119] will often cause the leucocyte count to rise to 14,000 per cubic millimeter. Larrabee, Tileston and Emerson[120] in a study of Marathon runners have shown that excessive exertion may bring this to 27,700 per cubic millimeter. The leucocytosis is polymorphonuclear in type. The final causation is quite unknown. The leucocytes are apt to increase in any part subjected to extreme slowing of the circulation, a point which is of possible value in the hyperemic treatment of various chronic inflammatory conditions.

Many *chemical agents* cause an immediate leucocytosis. Winternitz[121] studied such substances in detail. He showed just such a definite progression of effects as might be expected. Simple irritants induced a mild local reaction and very mild leucocytosis. Other more active irritants produced sterile pus and a high leucocytosis, a reaction differing in no way from that occurring with a bacterial abscess and attended by proliferative changes in the bone-marrow. Discussion of such leucocytoses has no place in this section, in which we have dealt with the minor, non-proliferative types of leucocytic increase with which the formative leucocytoses must necessarily merge. For a discussion of the chemical agents by means of which leucocytosis has been produced, the reader is referred to Ewing[121].

Finally leucocytoses of brief duration are found which are due to *bone-marrow disintegration*. The cells existing in the marrow are swept out together with the other elements as the tissue breaks down. Bunting[22] has pictured such leucocytic increases in rabbits following sharply upon injections of saponin and ricin. A leucocytosis occurring from marrow breakdown is characterized by finding many different marrow cells in the circulation, myelocytes, nucleated red cells, and even megacaryocytes. Such a phenomenon may occur preceding death and has probably been responsible for the designation "agonal leucocytosis." Disintegrative phenomena always give an extremely bad prognosis. They indicate an overwhelming onslaught upon the bone-marrow and are identified by the wholesale appearance of marrow elements. If the condition responsible for breakdown is characterized by a progressively falling leucocyte count indicating gradual white-cell aplasia in the marrow, the final agonal breakdown of the tissue may be signalled not by a leucocytosis but by a sudden appearance of whatever cells happen to be left in the marrow. Longcope[122], having noted the depletion of the marrow taken at autopsy in regard to polymorphonuclear leucocytes as compared with rib marrow resected during life, made an investigation of the changes in the bone-marrow in the terminal stages of acute infections. In many such instances the leucocytes in the blood often drop steadily until death occurs and may disappear almost completely from the marrow. Such a termination indicates gradual destruction of all the available leucocytes both in the blood and bone-marrow.

THE CONDITIONS INDUCING ACTIVE BLOOD CELL FORMATION

A. Conditions Inducing Change in the Number of the Erythrocytes and Blood Platelets

1. *Alterations in Barometric Pressure.*—It has already been shown that the position of the growing red cells in the medulla of bones assures their delivery into the circulation. Actual breakdown of the marrow tissue is the only condition, save growth, which will cause delivery of red cells to their final environment, the blood stream. In normal individuals formation and destruction of red cells are so perfectly balanced as to maintain a very constant concentration in the blood stream. As has been brought out, the total number of red cells in the circulation probably always includes a reserve utilizable in times of stress. The main function of the red blood cells is the carriage of oxygen. In less degree they carry carbon dioxide. For both of these functions hemoglobin is responsible, and it is in terms of the need for hemoglobin that the stimulus maintaining blood formation at its constant high level probably expresses itself. As has been pointed out we do not know whether adult red cells can increase their hemoglobin content. It is improbable that they can do so, and we must look for more hemoglobin not in terms of better old cells but in terms of more cells per unit volume of blood.

The normal equilibrium between red cell formation and red cell destruction maintains a red count of 5,000,000 per cubic millimeter or thereabouts. As Minot (Vol. II, Chap. XVI) brings out, this perfection of adjustment, which equips the individual for all ordinary needs, does not always exist and its absence may be unaccompanied by evidences of increased cellular breakdown or decreased formation. The patient is simply set at a low level and is usually very refractive towards any methods designed to produce improvement. If we understood the final nature of the stimulus causing red cell formation, it would be possible not only to treat such cases intelligently but also to apply more exact measures to the treatment of all anemias. Since hemoglobin is the essential substance of the red cells, an enormous amount of investigation has concerned itself with the physico-chemical properties of this substance. While such studies have great practical value in many directions they have yielded comparatively little information upon the cause of growth of the red cells. (The reader desiring a thorough exposition of the properties of hemoglobin is referred to the monograph of Barcroft[123].)

Paul Bert[124], in 1878, predicted that increase in altitude would be found to be accompanied by an increase in the oxygen capacity of the blood. In 1882, he confirmed this prediction, showing that the oxygen carrying power of the blood in animals living at high altitudes is much increased.

Viault[125], in 1892, completed Bert's work by showing that the blood of man in passing from a low to a high altitude shows an increase in the number of erythrocytes per unit volume of blood. Our interest in these facts lies in their application to the normal state of the individual. As we pass from a low to a high altitude we experience a lowering of the oxygen pressure in the atmosphere. Thus at sea-level the barometric pressure of 760 mm. of mercury is roughly 20 per cent. or $7.6 \times 20 \doteq 152.0$ mm. due to oxygen. Since the movement of oxygen from the pulmonary alveoli into the red corpuscles depends in the end upon this 152 mm. of pressure, we must naturally look for compensatory changes when it is reduced. Thus at an altitude of 6,060 meters the barometric pressure is 352 mm. The percentage of oxygen in the air at such a height remains as it was at sea-level but the partial pressure of oxygen is much reduced $3.52 \times 20 = 70.40$ mm. To achieve an adequate oxygen supply for the tissues under such conditions demands either a modification of the method by which oxygen is taken up by the blood in the lungs or else, the circulatory rate remaining constant, an increase in the number of corpuscles and hence an increase in the amount of hemoglobin passing through the lungs in a given period of time. In the last case the oxygen supply to the tissues is kept constant through the carriage of smaller amounts of oxygen by each of an increased number of corpuscles, while in the first case we must conceive of the development of a new power on the part of the lung cells so that oxygen is passed to the blood in adequate amounts although oxygen pressure relations are inadequate. It is possible that in passing to a high altitude both factors, increase in red cells and development of a power to secrete oxygen into the blood stream on the part of the cells of the pulmonary alveoli, are involved. We are certain of the increase in cells and hemoglobin. (The reader interested in the adaptation of the pulmonary epithelium is referred to the monograph of Haldane[126].) It is probable that this increase in cells expresses the action of the normal stimulus which keeps blood formation in steady progress and it is obvious from what has been said that oxygen want is the most outstanding factor involved. Loevenhart[127] and his collaborators have made the most recent studies of the effects of oxygen lack. They confined animals in chambers of varying size and under quite normal living conditions, save for alterations in the oxygen tension of the air breathed. The conclusions reached by these investigators are based upon such careful work as to leave no doubt of their validity. We quote them as they bear directly on the question in hand.

1. "A decrease in the oxygen tension of the respired air obtained by decreasing the oxygen concentration at atmospheric pressure or by reducing the barometric pressure stimulates the bone marrow and increases the erythrocytes and hemoglobin in the circulating blood in rabbits, white

rats and dogs. From five to seven days is required for the increase in the blood count to become very marked but the maximum increase requires a longer exposure.

2. "The increase in the erythrocytes and hemoglobin is absolute and not relative. We have been able to increase the total hemoglobin per kilo in rats 43 per cent.

3. "In order to produce these effects the oxygen pressure in the respired air must be reduced at least to approximately 14 per cent. of an atmosphere.

4. "The optimum oxygen pressure for increasing the oxygen capacity of the blood is apparently not far from 10 per cent. of an atmosphere.

5. "We have not been able to produce depression of the bone marrow by decreasing the oxygen supply. Stimulation results even when the oxygen pressure falls to 6 per cent. of an atmosphere.

6. "It is possible to stimulate the bone marrow to a certain extent by increasing the carbon dioxide tension of the respired air but it is not an efficient stimulus.

7. . . . .

8. "Our work indicates that the increase in erythrocytes and hemoglobin noted by practically all workers at high altitudes is due largely if not entirely to the decreased partial pressure of oxygen at high altitude, but the very rapid increases in the blood counts noted in man at high altitude and also the increases noted at comparatively very slight elevations are not explained by our work."

Douglas, Haldane, Henderson and Schneider[112] found an increase in hemoglobin in the first few days of residence on Pike's Peak. This they attributed to concentration of the blood through reduction in fluid. Schneider and Havens[128] in later work on Pike's Peak attribute this primary increase to movement in the circulation of a large mass of corpuscles which have been lying stagnant in large vessels. They also speak of loss of fluid and an early increase in the activity of the bone-marrow. It is possible that Loevenhart's failure to observe this early increase is attributable to the very quiet life led by his animals in contrast to the activity of men at high altitude. Actual new growth of red cells apparently begins at once and continues for several weeks. If the individual is normal the blood formation which occurs both under these conditions of high altitude and after hemorrhage seems to surpass his needs[94, 18]. He establishes a larger proportionate reserve than is needed and this true polycythemia is very persistent even though no need for it exists.

Figure 4 illustrates the manner in which increase in red cells and hemoglobin takes place on passing from residence at practically sea-level to residence on the top of Pike's Peak.

It is the rule that red-cell increase proceeds faster than hemoglobin increase whether in regeneration after hemorrhage or in proliferation to meet the demands of low barometric pressure. Exceptions to such a statement must of course occur. We count corpuscles of all ages in making such observations, and while adult erythrocytes probably cannot increase their hemoglobin content we unquestionably enumerate many very immature cells. With the exceptions of Gaule[129] and Schauman and Rosenquist[130], observers have failed to find nucleated red cells in the blood of men or animals subjected suddenly to low barometric pressure. Masing and Morawitz[131] found no increase in oxygen consumption on the part of their blood at a height of 10,000 feet. We have no statements as to reticulated cells, but this finding would indicate that few or any are present under such conditions. Even in the most radical experiments on oxygen reduction, Loevenhart[127] reports very limited changes in the blood picture.

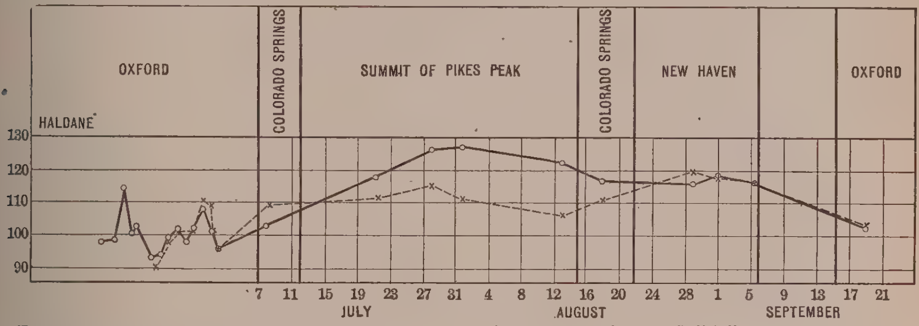

FIG. 4.—Variation in red cells and hemoglobin at different elevations. Solid line, red cells; broken line, hemoglobin.

"Blood smears from animals showing increased blood counts after exposures to atmospheres poor in oxygen when stained with Jenner's stain show a number of basophilic erythrocytes. This staining reaction is characteristic of newly formed erythrocytes. Many of these basophilic erythrocytes were abnormally large, especially in those animals which showed a marked increase in the hemoglobin without very much change in the number of erythrocytes. This probably explains the increase in the amount of hemoglobin per corpuscle in certain cases."

The views upon extrusion of red cells from the marrow, which have been presented, explain the finding of nucleated red cells in the blood stream on the basis of overcrowding in the marrow. The stimulus of low barometric pressure always acts more temperately than does that of severe hemorrhage. While observations in plenty show that marrow growth takes place under the former conditions, it apparently does so slowly enough to permit absorption of fat and bone so that growth produces no overcrowding, and only mature erythrocytes reach the circulation. The leucocyte count may rise slightly as this deliberate new formation occurs but the change is of little importance. Kemp[132] has shown that the platelets increase markedly. Loevenhart's failure to find proliferation of red cells until the oxygen had been reduced to 14 per cent. of an atmosphere, or to a partial pressure of 106.4 mm., is interesting in view of the fact that Barcroft[123] found no reduction in the CO_2 tension of the alveolar air until practically the same conditions were experienced. In a number of individuals he reports no significant change in the alveolar CO_2 tension until an altitude of 10,000 feet is reached. At this height the barometric pressure is 530 mm. and the partial pressure of oxygen, 106 mm. It seems therefore, that the individual is so equipped as to meet altitudes up to the neighborhood of 10,000 feet without any large change in his blood formation. But on reaching such an elevation increased blood formatoin is at once found and accompanying this formation there is a reduction in the CO_2 tension of the alveolar air. As Barcroft[123] has shown this CO_2 is probably replaced by another non-volatile acid.* The question at once arises whether what we call acidosis can in itself be responsible for blood formation. Loevenhart has shown that atmospheres high in CO_2 may increase the hemoglobin and red-cell count to a very slight degree but the changes he records are too little to be significant in the abence of concomitant records as to blood volume. It is of course possible to get evidence of acidosis in many cases in which blood formation is taking place but at present we have no evidence that this factor is in any important way a stimulus to red-cell formation.

Finally, the fact that Loevenhart could not depress the marrow by extreme decreases in the oxygen supply is worthy of comment. Apparently as long as men or animals are eating a mixed diet and thoroughly assimilating their food, none of the conditions bringing about blood formation can be pushed to the point of depressing the marrow. The red count in dogs can be reduced to 4,000,000 by means of a diet of rice alone[33], but neither reduction of barometric pressure nor persistent bleeding can render the marrow aplastic unless accompanied by extremely deficient food.**

The effect of low barometric pressure on blood formation has been discussed first because it is the simplest both in result and in character of the conditions inducing formation. Oxygen want is the easiest explanation for the change and at present must satisfy us. Short of direct toxic action the most successful efforts to produce marrow aplasia are those of Robertson[133] who made rabbits polycythemic by successive intravenous injections of red corpuscles. As a result of this addition from without, the need for corpuscular formation was removed and marrow aplasia appeared.

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* For recent views upon anoxemia and related conditions see Haldane, J. S.: *British Medical Journal*, 1919, II, 65.

** Recent work upon the relation of diet to the production of anemia will be found in the following papers: Whipple, G. H.. and Hooper C. W.: *Am. Jour. Physiol.*, 1918, XLV, 573 and 576.

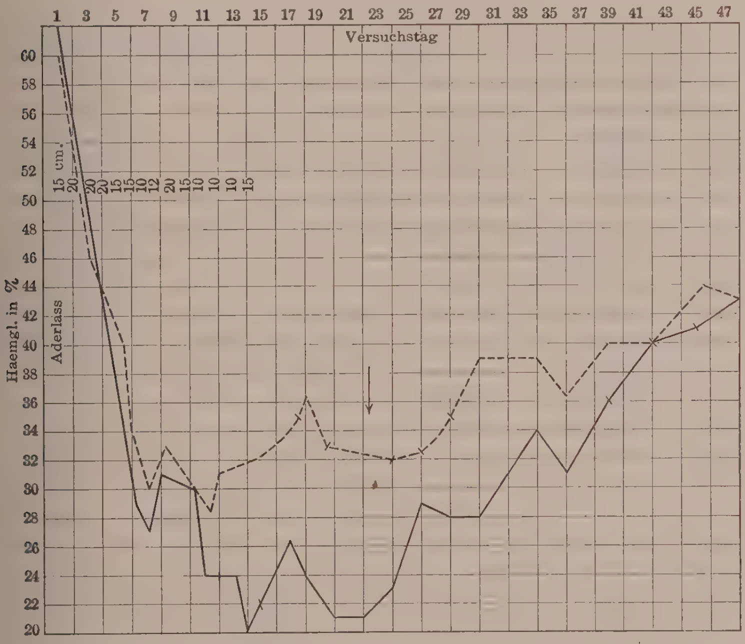

FIG. 5 (a).

2. *Hemorrhage, Acute and Chronic.*—In the foregoing section we have covered a condition of anemia which is suddenly imposed on the individual by his surroundings. The course of events in meeting the effects of high altitude is, however, somewhat different from that undergone in the case of blood loss. In the first instance there is a moderate reduction in blood volume serving to concentrate the cells, and only later, when actual cellular proliferation is in progress, does blood volume increase. Following hemorrhage, however, we have an immediate tendency to restore blood volume. Fluid flows rapidly into the vessels, dilution of the blood occurs, and regeneration commences. This regeneration is so vigorous that one can frequently find abnormally young red cells in the circulation even after moderate hemorrhage, whereas the only evidence of red cell forming activity in moving to high altitude may be a very gradual increase in red

cells and hemoglobin. Masing and Morawitz[131] illustrate this point. A loss of 400 c. c. of blood caused a prompt increase in the oxygen consumption of Masing's red cells, indicating prompt movement of immature forms into the circulation, while a residence of one week at a height of 10,000 feet made no such impression.

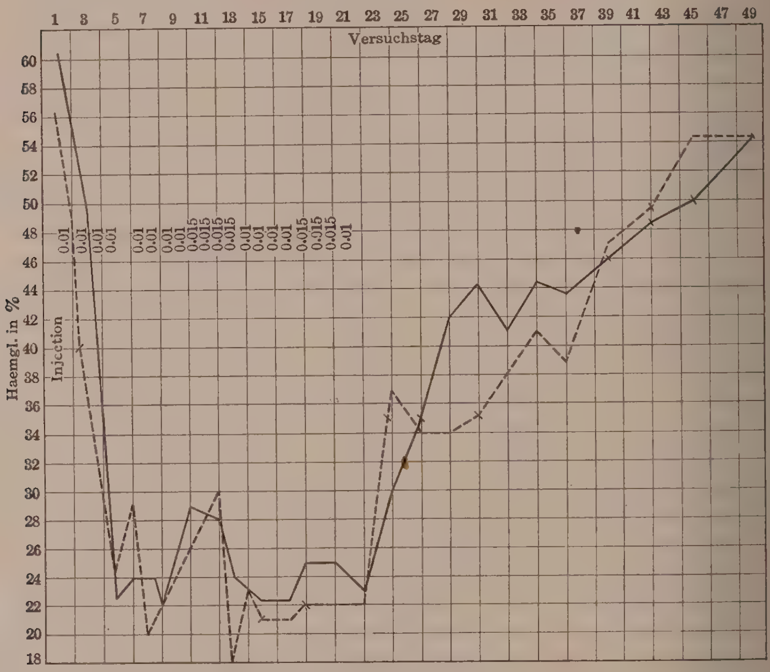

FIG. 5 (b).

Many efforts have been made to show that regeneration after hemorrhage involves other factors than oxygen lack and the progress of events which may follow in its train. Carnot[134] injected the serum of anemic dogs into normal animals and announced that he obtained an increase in red cells. No one has ever been able to confirm his observations[135]. Blumenthal and Morawitz[136], Itami[137], and Ritz[138] found that blood regeneration proceeded more vigorously in anemias caused by phenylhydrazine than in anemias due to hemorrhage in which the blood was actually lost. Figure 5 (a) and (b) illustrates this point. They present further evidence to show that injection of the lost blood into the peritoneal cavity removes this difference. Morawitz[135] suggests that the products of red-cell breakdown may stimulate formation and Kepinow[139] on injection of blood-cell lipoids got accelerated recovery from experimental anemia. It is possible that the stimulating effect of blood transfusion in anemia is due to the factors above noted. Finally, Krumbhaar and Musser[97], following observations by Danilewsky[140] and Silvestri[141], record a transient increase in red cells following intraperitoneal injection of extracts made from fresh spleen. It is apparent that the extreme difficulty of control involved in all these experiments renders their interpretation difficult. They are mentioned since they are more positive than results reported from the administration of bone-marrow and bone-marrow extracts.

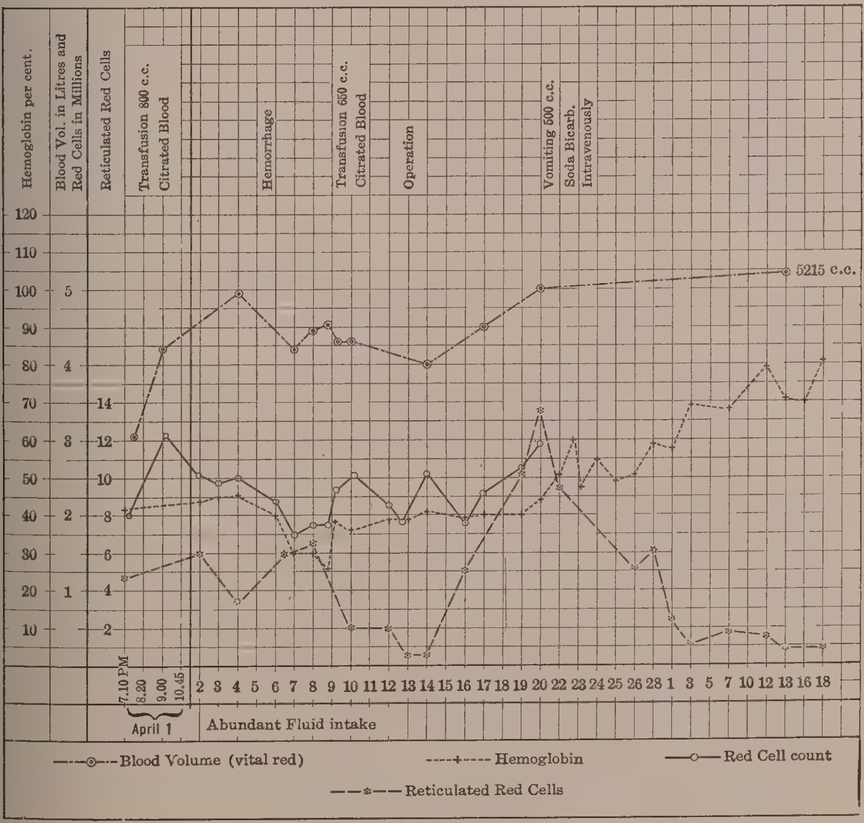

FIG. 6.

The regeneration of red cells following hemorrhage has been followed more carefully in animals than in man. Fig. 2 pictures regeneration in a dog subjected to nine large hemorrhages. Unfortunately this curve is unaccompanied by blood-volume determinations. It is adequate for the purpose it was designed to fill; *i.e.*, the delineation of the time at which immature red cells might be found in the circulation, but it fails to show with accuracy certain features in regeneration. Robertson and Bock[142] have recently published very complete observations upon traumatic hemorrhage. Fig. 6 is a slightly simplified expression of their findings. In this patient transfusion holds the blood volume rather constant. Note the large increase in reticulated cells which occurs just prior to the increase

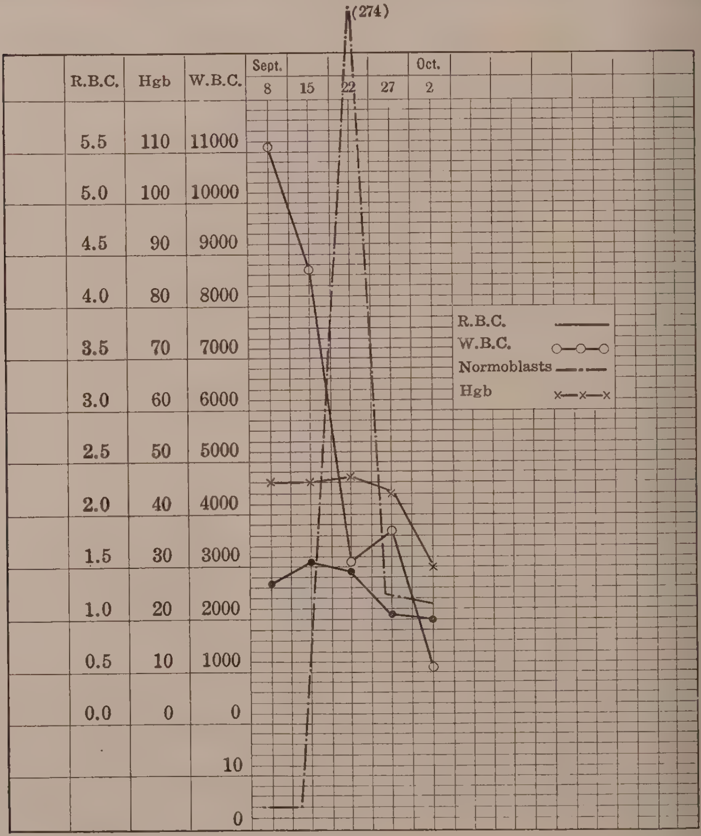

Fig. 7.

in red cells and hemoglobin. Such a crisis of reticulated cells is of good portent and is a more delicate index of promised red-cell increase than is a crisis of nucleated red cells. Fig. 2 pictures crises of nucleated red cells. If one follows the curve of these cells it will be seen that there are occasional increases immediately following the hemorrhage. These merely indicate a thorough stirring up of the blood already in the vessels and have nothing of promise for red-cell increase. The true formative crises are easily made out and their relation to improvement in the blood picture is obvious. Such crises are of short duration and indicate more rapid bone-marrow proliferation than the available marrow space permits. As time passes, if blood loss is repeated, crises are less and less apt to occur. It has been pointed out that nucleated red cells alone are capable of forming other red cells. Mitoses in nucleated cells are often seen in severe anemia, and naked nuclei are often found. The mitotic cells indicate that division sometimes occurs in the blood stream and it is possible that loss of the nucleus also

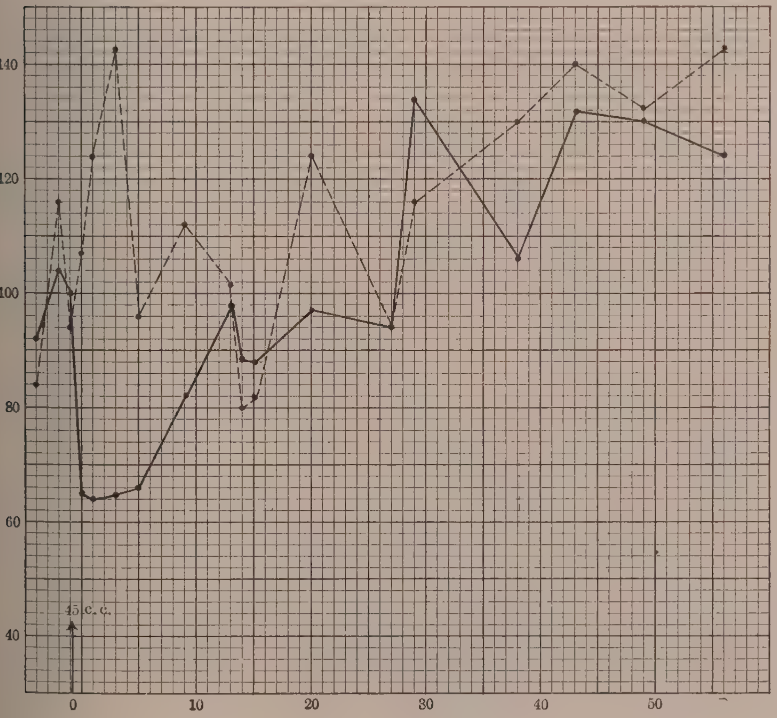

FIG. 8.

takes place. We, however, have no direct knowledge as to what becomes of the thousands of nucleated red cells which occasionally flood the circulation. While normoblast crises are practically always followed by betterment in the simple anemias due to hemorrhage which we have been discussing, they may have quite the reverse outcome in the pathological anemias. Fig. 7 illustrated the blood findings in a case of severe pernicious

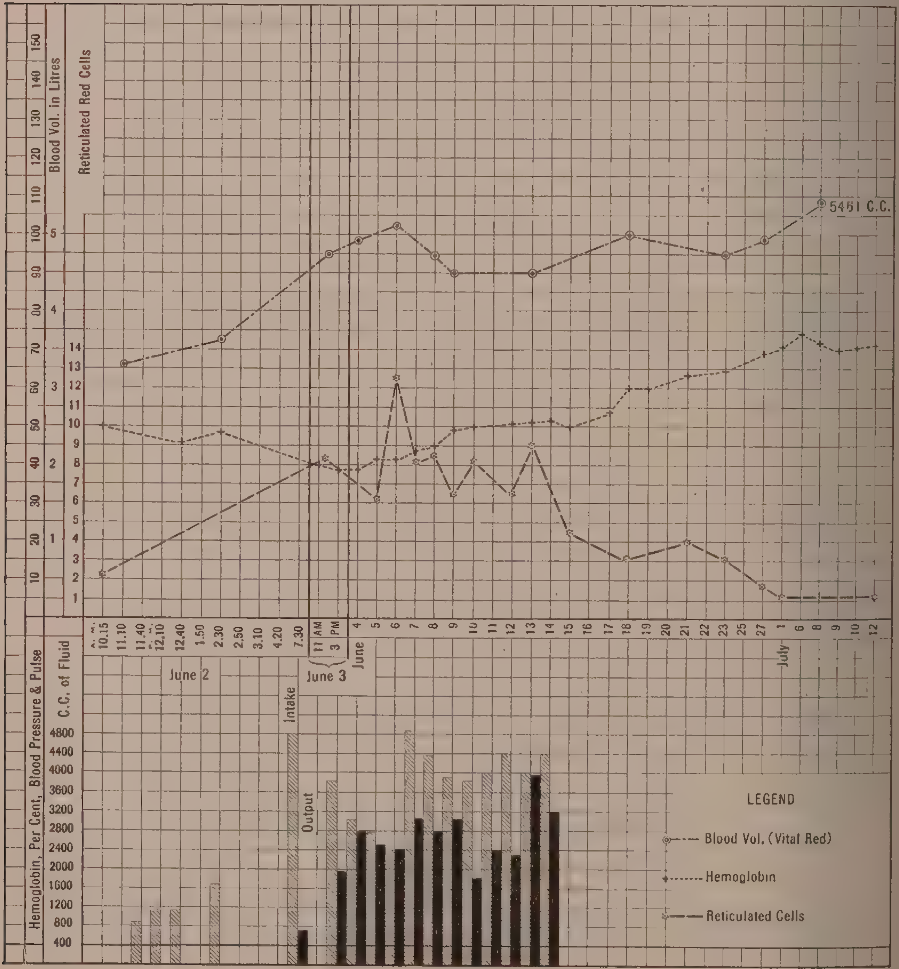

FIG. 9.

anemia which terminated fatally on the tenth day following a large crisis. The bone-marrow from this individual was almost entirely lacking in myelocytes and polymorphonuclear leucocytes but still contained a large number of nucleated red cells and many small megacaryocytes.

Fig. 8 indicates the course of regeneration of hemoglobin in a rabbit suffering a single large hemorrhage. Note the sudden large increase in blood volume with a gradual building up of hemoglobin to meet it. Robertson and Bock[142] in Fig. 9 indicate the slowness with which blood volume may be restored unless fluids are available. Obviously the conventional red counts and hemoglobin estimations made some time after hemorrhage in such a case would give little idea of the severity of the blood loss. Following hemorrhage, in addition to the restoration of blood-cells, there must be a restoration of plasma protein, the details of which are beyond the scope of this chapter. Readers desiring recent information upon this phase of blood formation are referred to papers by Whipple, Hurwitz and others[143].

Thus far in the discussion of cellular regeneration after hemorrhage it has become apparent that marrow activity is foretold by the appearance of reticulated and nucleated red cells. Synchronously with these, many polychromatophilic forms will be found and there will be an increase in platelet count. A million platelets per cubic millimeter, and these of small size, is a frequent accompaniment of proliferation after hemorrhage. The granular leucocytes in the blood stream increase very markedly in the hours immediately following hemorrhage. This increase is polymorphonuclear in character and is often maintained for several weeks. During normoblast crises myelocytes are often quite numerous and the total leucocyte count may rise. The lymphocytes are not affected by blood loss. Those which can disappear in any bearable hemorrhage are apparently made up by so slight an increase in the activity of the lymphadenoid tissue as to be indistinguishable.

Changes in shape and size of the red cells are not ordinarily marked following a single hemorrhage, even though very large. In chronic hemorrhage, however, there may be extensive poikilocytosis and anisocytosis. As a rule the abnormal red cells following hemorrhage tend toward small rather than large forms and there is an absence of minute fragmentation forms. Minot, in the subsequent chapter on anemia, calls attention to the prominence of large oval red cells in pernicious anemia.

3. *Alterations in the Character of the Hemoglobin.*—Alterations in hemoglobin which prevent combination with oxygen may place the individual in much the same position as does sudden reduction of barometric pressure. In the latter instance physical conditions prevent the individual cells from gaining their proper quota of oxygen, while in the former each cell may

suffer change in hemoglobin which prevents oxygen transport. The commonest defect of this type is caused by carbon monoxide which combines very readily with hemoglobin and thus prevents oxyhemoglobin formation. Red cells completely saturated with carbon monoxide will gradually give off this gas under normal barometric pressure and will regain their power to take up oxygen. Apparently a number of cells will regularly fail in this test and go permanently to pieces. As a result we must look upon blood regeneration following carbon monoxide poisoning as referable to two causes, interference with the oxygen carriage through formation of carbon monoxide hemoglobin, and actual red-cell destruction. It is true that evidences of red-cell destruction from carbon monoxide are all obtained from poisoning by illuminating gas which contains many substances besides carbon monoxide. Nasmith and Graham[144] have shown that guinea pigs kept in an atmosphere of water gas increase their red-cell count per cubic millimeter quite rapidly, and that, if poisoning is pushed or is much prolonged, nucleated red cells and myelocytes are numerous in the peripheral blood. Unfortunately their experiments do not include blood volume estimations. If carbon monoxide is administered carefully a condition of chronic polycythemia may result with extension of blood-forming tissue through the shafts of the bones and elsewhere. The state of the animal may thus simulate high altitude effects very exactly.

In addition to carbon monoxide hemoglobin, one other hemoglobin alteration occurs quite frequently during life. Many drugs, such as potassium chlorate, acetanilid, etc., cause methemoglobin formation. Methemoglobin can be transformed to hemoglobin by reducing agents, but it is probable that red cells containing this substance are never transformed back into normal functioning elements. Apparently most of the methemoglobin which is formed is excreted in the urine. If administration of any of the substances causing methemoglobin formation is pushed, active cellular breakdown occurs with marked methemoglobinuria. Curves of blood regeneration in such instances are well typified by Fig. 5 where phenylhydrazin has been the causative agent.

B. Condition Inducing Change in the Number of the Granular Leucocytes

1. *Leucopenia and Leucocytosis Accompanying Toxic Injections and Infections.*—In previous sections we have taken up the general character of the granular leucocytes, the manner in which they leave the bone-marrow, and finally certain alterations in their number in the blood stream which are not associated with new formation. It remains to discuss the character of the stimuli bringing about leucocytosis, the duration of such reactions, and factors which conceal or inhibit them.

"Leucocytosis" now means increase in the polymorphonuclear neutrophils in the blood stream. Eosinophilia and lymphocytosis should always be mentioned under their special names. The function of the polymorphonuclear neutrophil is directed almost entirely toward the removal of infection or toxic injection. To a moderate degree these cells assist in blood coagulation but they exhibit no more specialization in this direction than do many other body cells.

There is scarcely a substance which can be injected subcutaneously without producing leucocytosis. It will often be found that simple hypodermoclysis with physiological salt solution acts in this way. Similarly turpentine and oily substances in general will induce leucocytosis. But the action of such substances depends on the production of local tissue injury and the transfer of something from this area to the bone-marrow. In order to test the leucocytosis-producing effect of any substance it is, therefore, necessary to introduce it directly into the blood stream. When this is done it is found that proteins in general will cause leucocytosis. Thus bacteria and their extracts are very potent. Proteoses, peptones, albuminous fluids of all sorts, nucleo-proteins, and a host of extracts from various organs containing mixtures of many different proteins, have all been found to produce a fairly definite train of events when introduced directly into the blood stream. Variations in the grade of effect are of course noted. These depend not only on the character and amount of the substance injected, but also on the condition of the leucocyte-producing tissue in the animal at the moment of injection.

A characteristic result of such injection is as follows[145]:

Rabbit 1101, injected Nov. 1 with half agar slant of live B. typhosus. Before injection the leucocytic count is 14,000.

Hours after Injection	*Number of Leucocytes*
1	2,000
2	900
4	1,600
6	2,800
8	8,600
10	9,200
12	10,300
14	16,600
16	14,800
18	11,400
20	15,200
22	18,700
24	14,600

If dead typhoid bacilli are given intravenously to man a similar reaction occurs. In this case the period of leucopenia may be so short as to escape observation[146]. It is, however, always found if the observation is close enough. It is sometimes stated that immediately following the injection there is a transient leucocytic increase followed by leucopenia and then a persistent leucocytosis. The primary increase is at best insignificant and lies within the possible error of counting, so that we are justified in listing the phenomena following intravenous injection of typhoid bacilli as a leucopenia of brief duration followed by leucocytosis. Similar phenomena follow injection of other proteins.

The first description of leucopenia following bacterial injection was given by Werigo[147]. Löwit[148] examined the same phenomena and was followed by Goldscheider and Jacob[149]. Two theories of the leucopenia arose as a result of the work of these and other investigators: (1) the leucopenia is due to actual destruction of leucocytes; (2) the leucopenia is due to a sifting out of the leucocytes in various capillary areas.

Löwit's[148] contention that leucocytes are actually destroyed as a result of such injections has not been confirmed. The second possibility[150] has received very thorough examination. Bruce[150] counting the leucocytes in sections of the lung, spleen, and liver of animals in the leucopenic phase following peptone injections found a marked increase in number as compared with normal animals. Muir[150] and Silverman[150] confirmed this observation, but no satisfactory reasons have ever been given why accumulation of leucocytes occurs in these organs. Wells[150] made very careful counts in many different areas during leucopenia and arrives at the following conclusions which, as will be seen, differ from former observers in regard to the lungs.

"Within a few minutes following the intravenous injection of dead bacteria into rabbits there results a marked decrease in the number of leucocytes in the circulating blood, resulting in a condition of leucopenia.

"The decrease in the number of leucocytes involves chiefly the polymorphonuclear elements, in some cases these cells practically disappearing from the circulating blood.

"Blood obtained from the splenic and hepatic parenchymata during leukopenia contains an enormously increased number of leucocytes per c. mm., as well as an increased number and proportion of polymorphonuclear elements.

"Blood obtained from the lung parenchyma during leucopenia does not contain an increased number of leucocytes, tho sections during this stage show a slight hyperemia and increase of these cells.

"Blood from the bone marrow during leucopenia contains a normal or increased proportion of polymorphonuclear elements, with usually a somewhat increased total number of leucocytes.

"Living organisms injected intravenously may be found in the liver and spleen a few minutes after the injection, synchronously with the onset of leucopenia.

"The finding during leucopenia, of injected living bacteria in the spleen and liver, synchronously with a great increase of polymorphonuclear leucocytes in these organs, and a great decrease of these cells in the general circulation, suggests that leucopenia is best explained on the basis of a positive chemotaxis.

"Hyperleucocytosis is the result of the discharge from the spleen, liver, and perhaps other organs, of the leucocytes accumulated therein during leucopenia, plus the new cells produced in the bone marrow.

"During hyperleucocytosis the blood from all sources in the body shows a great increase in the number and proportion of the polymorphonuclear leucocytes."

Wells[150] thus believes that injected bacteria sift out in certain organs and are promptly followed there by the leucocytes which are in circulation at the moment. As these cells leave the circulation there is a steady pouring out of mature forms from the bone-marrow to take their places and finally the leucocytes which have moved after the bacteria into the liver, spleen, etc., begin to come back into the blood stream, resulting in a great increase. That bacteria do tend to accumulate in certain organs when introduced intravenously has confirmation in the work of Bull[151], who found that injected typhoid bacilli disappear from the circulating blood in fifteen to twenty minutes and may be found in sections of the liver and spleen and to a less degree in other organs. Why bacteria should so congregate is, as we have said, unknown and whether other large protein molecules, such as peptone and hemoglobin, collect in the liver and spleen in a similar way to be attacked there by leucocytes is entirely problematical. Sellards and Baetjer[152] have suggested the possibility that this is true and propose using the leucocytic accumulations as criteria of the distribution of injected albuminous material.

The transient leucopenia, which we have just discussed, apparently expresses the movement of leucocytes toward areas where they can be of most service. It is clear that very slow injection of protein will not produce such a leucopenia since leucocyte formation and extrusion from the bone-marrow, together with passage back of leucocytes into the blood stream from the liver and spleen, will mask any diminution which tends to occur. The probabilities are that acute leucopenia is never seen in connection with naturally acquired infections unless the circulation is flooded suddenly with bacteria. If close observation shows that blood cultures have become suddenly very positive, a diminution in circulating leucocytes may be observed to accompany this change and signals, just as in the case of bacterial or simpler protein injections, withdrâwal of leucocytes from the circulation toward the more important sites of bacterial collection. A leucopenia such as this would be transient and would be followed by leucocytosis as a favorable phenomenon. If, however, the number of leucocytes takes a steady downward course, as is sometimes seen in fatal pneumonias and infections with streptococci and staphylococci, the observer may understand that actual leucocyte destruction is in progress accompanied by advancing aplasia of the marrow. Such a course is of bad import and was very frequently seen during the influenza epidemic of 1918–1919. Dickson[16] has pictured marrows overwhelmed by fatal infections.

Certain diseases, of which typhoid fever is the most notable example, are ordinarily accompanied by a leucopenia throughout their entire course. When typhoid runs a normal course there seems to be no tendency for leucocyte formation in the marrow. Those cells which are there at the moment of infection are apparently gradually used up and there is little new formation. The organism, however, may at once begin to form leucocytes very actively if infection of another type takes place as, for instance, in the event of intestinal perforation. We as yet have no understanding of the further facts that abnormal types of typhoid infection, such as typhoid osteomyelitis or empyema, cause leucocytosis quite readily. Similarly, in the case of tubercle bacillus, there is little or no tendency to leucocytosis unless meningitis occurs. Leucocytosis, therefore, seems to have some relation to the degree to which infectious processes are localized. In a case of malignant endocarditis due to a streptococcus, blood cultures may be positive on repeated examination. Organisms are evidently being washed constantly into the blood stream. In such a case of persistent blood infection the leucocyte count is usually low, as though the leucocytes which reached the blood stream were constantly leaving it to phagocytize organisms drained out in different situations.

The speed with which leucopenia or leucocytosis may develop is a frequent source of surprise. Following intravenous injections of protein. leucopenia of profound character may be found within ten minutes, and that this represents the condition of the blood all over the body can easily be demonstrated by withdrawal of capillary, venous and arterial specimens. If the bone-marrow is examined at the same time a slight increase in leucocyte content will be made out. Let us suppose that the injection consists of living organisms which, through their multiplication, demand a persistent resistance on the part of the host. There ensues a steady migration of leucocytes back into the blood stream and concomitantly a leucoblastic transformation of the marrow. In the case of the erythrocytes the marrow is not a reservoir. It is constantly delivering its total available product to the circulating blood. On the other hand, the marrow acts as a reservoir for the leucocytes and alterations in their number in the peripheral blood mean first of all a draining of the available supply through extension of the leucocyte-forming tissue. It is not possible to say whether the stimulus for extension of leucocyte-producing tissue lies in the simple depletion of the marrow or in the action of the substance causing leucocytosis. Most probably the latter explanation is the true one. Within forty-eight hours after injections of Staphylococcus pyogenes aureus in rabbits, Roger and Josué[153] found marrow hyperplasia but note that at first it is confined mainly to red cell producing tissue. It is probable that these authors have simply misinterpreted the findings which such marrow presents. There is a preliminary intense congestion followed by the appearance of larger and larger areas of leucocyte-forming tissue. Synchronously the fat and bony spicules begin to disappear, the process of removal being most active at the ends and periphery of the medullary cavity and gradually extending until practically all the fat in the shaft of the bone may be replaced.

In considering these changes, which may move forward with great rapidity, the reader must recollect that growth pressure probably soon becomes the chief cause for forcing leucocytes into the circulation and that younger and younger forms may thus make their appearance. Arneth[154] has studied the neutrophilic leucocytes in infections of varied type and has attempted to classify them in accordance with the number and shape of the nuclear segments. As the nucleus appears less and less lobulated he argues that younger and younger forms are being observed. Since these young forms are less phagocytic than the adult multilobed neutrophils, Arneth believes that a blood picture containing a predominance of them, while it may mean very florid leucocyte formation, does not indicate a favorable situation for the patient since it would seem that his adult cells are being too rapidly used up. While Arneth's contentions and evidence are apparently reliable, his count is too cumbersome to be of much value. It gives no information about disease progress which cannot be equalled by more exact methods of other types.

Just as leucopenia and leucocytosis may develop very rapidly, so with equal rapidity do they seem to disappear. There is little tendency for leucocytosis to persist after infection has subsided. It will be maintained as long as the organism successfully combats infection but will disappear promptly on the removal of the stimulus for its causation. Leucoblastic transformations of the marrow are thus far less stable than those of erythroblastic character which subside very sluggishly when their need has been removed.

2. *Post-Hemorrhagic Leucocytosis.*—There are few biological reactions which may be so fully relied upon as the leucocytosis following hemor-

rhage[13]. Beginning within ten minutes of blood loss and reaching its height in about two hours, there is an invariable increase in the polymorphonuclear leucocytes. This change will occur, whether or not the animal receives an infusion of any sort to restore blood volume, and it is independent of the wound attending the hemorrhage. Apparently the very rapid flow of tissue juice into the blood stream which follows hemorrhage carries with it protein material foreign to the blood stream, and leucocytosis necessarily ensues. Following a single large hemorrhage, the leucocyte count may remain high for a week. The leucocytosis of hemorrhage is often confused with the moderate leucocytosis which follows operations[155], and which, being due to material absorbed from the healing wound, is roughly parallel to the extent of the wound.

3. *The Leucocytosis of Pregnancy.*—During pregnancy the leucocyte count in two-thirds of the cases will reach a level of 13,000 to 16,000 per cubic millimeter[156]. It is probable that this slight increase, which disappears within two weeks after delivery, signals a constant existence in the circulation of the mother of small amounts of protein material abnormal for her. Whether this material is derived from the fetal membranes, the fetus, products of maternal digestion, etc., is not known.

4. *Eosinophilia.*—In a previous section the question of the origin of the granules which distinguish these cells has been covered, and we have indicated that, in this disputed field, there are no facts which successfully explain the appearance of eosinophilia in the different circumstances under which it is found. Eosinophils increase in the blood stream in many cases of myelogenous leukemia, in bronchial asthma, in certain skin diseases, and notably in infection by intestinal parasites. Trichinosis presents the most marked examples of eosinophilia, excepting of course the extreme eosinophilic increases which may occur in leukemia. Since the common custom of gauging eosinophilia through the differential leucocyte count leads to many mistakes, Emerson[157] advocates an absolute enumeration of these cells and believes the count should rise above 250 per cubic millimeter before eosinophilia is considered to exist. In a normal adult with a total white-cell count of 7,000 per cubic millimeter this would mean that a percentage above 3.6 indicated absolute increase.

Opie[49] has studied the development of eosinophilia in guinea pigs after administration of Trichina spiralis and finds that increase in eosinophils does not occur until trichinae begin to pass to the muscles. Owing to the fact that normal animals seem to possess no reservoir of fully formed eosinophils, the total number increases through some days, during which time there is an extensive proliferation of eosinophils in the marrow. If trichinal infection is very severe there is a disappearance of circulating eosinophils with degeneration of those in the bone-marrow. Opie[49] has shown that in the same animals eosinophils move from the bone-marrow into the blood stream and from the blood stream to sites of bacterial inoculation, but that, though behaving in these respects like neutrophilic leucocytes, they rarely act as phagocytes.

C. Conditions Inducing Change in the Number of the Endothelial Leucocytes

The condition under which endothelial leucocytes increase in the peripheral blood have been difficult to enumerate because of the question which arises constantly as to the identity of particular cells. McJunkin[158] has taken advantage of the fact that these cells phagocytize non-protein particles such as carbon with far greater avidity than do any of the other white blood-corpuscles. He has enumerated them after giving opportunity for carbon ingestion, and has also developed a method for their identification through a staining reaction. McJunkin[158], in thirty-four differential counts made in accordance with his methods, finds the endothelial leucocytes make up 5 per cent. of the total number of white cells. Evans[64] noted a great increase in these elements in one case during a severe reaction following salvarsan administration, a finding which has not been repeated and which seems referable to some peculiarity in this individual. The case reported by Van Nuys[63] had palpable tumor masses in the abdomen and unfortunately the nature of these was never made out. This patient showed as many as 46,000 endothelial leucocytes per cubic millimeter. These cells were somewhat phagocytic for the other blood-cells. The case reported by Bartlett[63] and in more detail by Rowley[65] showed no evidence of neoplasm, admission to the hospital being for cardiac disease. In this instance the increase in endothelial leucocytes was not so great as in the case reported by Van Nuys[63] but phagocytosis of the other varieties of blood-cells was even more marked. There is no explanation in any of these cases as to the source and function of the cells in question. Bunting[159] has found a constant slight increase in endothelial leucocytes in Hodgkin's disease. Naegeli[13] has found them increased in tuberculosis of the lymph-glands and Warfield[160] has reported an increase in a fatal case of typhoid fever. This last finding is quite unusual and indicates the lack of specificity which seems to characterize the appearance of these cells. With exception of Hodgkin's disease, there is no single condition characterized by the appearance of endothelial leucocytes in the blood stream. It is possible that through the methods introduced by McJunkin[158] their identification may be rendered easier and their relation to disease more definite.

D. Conditions Inducing Change in the Number of the Lymphocytes. Relative and Absolute Lymphocytosis.

Clinical statements as to the existence of lymphocytosis depend too frequently on simple differential counts, and it will be well, as in the case of eosinophilia, to give an absolute enumeration of these cells before making deductions as to the condition of the blood in question. Relative increases in lymphocytes will accompany practically any of the polymorphonuclear leucopenias. Thus, if one follows the lymphocytic content of the blood in typhoid fever a relative lymphocytosis will be found which, however, during the second and third week of the disease will gradually become a low grade absolute lymphocytosis. It is such transitions as these which depend for their detection on absolute counting of the cells in question.

At birth the lymphocytes make up 50 to 60 per cent. of the circulating white cells. During normal growth of the child this gradually is reduced and reaches the neighborhood of 20 per cent. by the fifteenth year. During all these early years the lymphocytes are absolutely increased and their slow decrease is an index of normal development. It is noteworthy that almost anything which interferes with the proper growth of the child may arrest the decrease in lymphocytes which should occur, and may be signaled by an increase in their number. Thus, rickets, and malnutrition attendant upon any set of circumstances, are almost invariably attended by moderate lymphocytosis. These conditions in childhood seem, however, to operate more toward the arrest of lymphocyte disappearance than to actually stimulate increase. Should they operate in the latter way, lymph-gland overgrowth is apt to become apparent. In the case of the lymphocytes, as in the case of the granular leucocytes, active growth of young cells in the lymphoid tissue is apparently necessary in order to force them into the circulation. Recent studies by Murphy[161] and his associates are of interest in this relation. These observers have shown that moderate exposures to dry heat and to X-rays result in lymphocytosis and that this is accompanied by active division of cells in lymphocyte-bearing tissue. Taylor[161] citing the observations of Wickline[162] and of Chamberlain and Vedder[163], who found lymphocytosis in soldiers on duty in the Philippines, was able to show that in twenty-five of thirty-eight individuals subjected to ordinary sunburn there was a decided absolute lymphocytosis. The lymphocytosis as a result of dry heat obtained by Murphy[161] in mice has, so far as we know, no confirmation in man. The number of lymphocytes in the circulating blood will usually be found to correspond very directly with the amount and activity of growth of lymphoid tissue. Many infections seem to have stimulating effect on this tissue. In childhood practically any infection will result in lymphocytosis. Thus, diphtheria, whooping cough, measles, scarlet fever, bronchopneumonia and chronic diarrheas are apt to show varying grades of lymphocytosis. Murphy and his associates[83] have directed attention to the fact that resistance to tuberculosis depends to a marked degree upon the lymphocytes. There seems to be no doubt as to the truth of this statement but, as these workers indicate, it is a hard one to correlate with the fact that lymphoid tissue represents one of the commonest sites of development of tuberculosis.

When lymphocytosis develops in the course of human infection the reaction is not apt to proceed so abruptly as in the case of leucocytosis. Even though growth of lymphoid tissue may be rather vigorous, its surroundings are not so favorable for immediate and large impressions upon the circulating blood as in the case of the leucocytes and red cells. The exception to this statement occurs in certain instances of tumor growth when the circulation may be rapidly flooded with small round cells which in appearance are lymphocytes but which in reality are tumor cells.

A final point of interest in relation to lymphocytosis is the frequency with which this condition is accompanied by slight eosinophilic increase. Neither of these types of cells tends to increase in the face of neutrophilic leucocytosis but in slowly developing lymphocytosis we are almost certain to have a tendency toward eosinophilia. No reasons for this relation can be given.

BLOOD DESTRUCTION

Destruction of the Erythrocytes

That regeneration of the erythrocytes keeps pace most accurately with the normal wearing out of these cells is a self-evident fact, but though we readily appreciate the consequences of increased red-cell destruction and though we can detect even minor increases in the process, we are still in the dark as to its exact nature. It is simple enough in the presence of hemoglobinuria to understand that hemolysis has recently occurred, but hemoglobinuria is a pathological finding and in the daily loss of red cells which every normal individual must experience no such extreme evidence of loss is allowed to escape. So far as we know at the present time the unaltered products of hemolyzed red cells are invariably toxic, causing some grade of fever and being apparently excreted as promptly as possible. The normal fate of the erythrocyte is unattended by any such phenomena and we may, therefore, in searching for its character look toward methods of removal which do not permit the freeing in the blood stream of hemoglobin nor erythrocytic stroma.

A. Phagocytosis

Rous and Robertson[164] have reviewed and amplified the subject of red-cell phagocytosis. They have found that "phagocytosis of red corpuscles, while frequent in the normal dog, rat, and guinea pig, is slight in man, the rhesus monkey and many rabbits. In cats it is always negligible in amount and frequently absent. Phagocytosis will not suffice as a general explanation of normal blood destruction." The statements made are not attended by any indication as to the amount of human material studied, and while it is probably true that this method of red cell removal is not the most important in man, attention may again be directed to the cases of Rowley[65] and Van Nuys[63] in which cells, apparently identifiable as endothelial leucocytes, were observed to be actively phagocytic for red cells. It is true that both of these cases present extreme abnormality but they none the less indicate a tendency which under normal conditions is probably operative to some degree. Pearce and Austin[165], in 1912, remark that, with the exception of the facts that large endothelial cells, principally splenic, phagocytize red cells and that the Kupffer cells of the liver occasionally contain hemoglobin or some derivative of it, we have no definite knowledge as to phagocytic destruction of erythrocytes. To the sites just given we may add the bone-marrow and certain lymph-glands, in both of which positions endothelial phagocytes present varying degrees of activity in the ingestion of red cells and blood pigment. It is of interest to note that in rabbits receiving daily injections of blood there is no apparent increase in phagocytic destruction of red cells, though other methods for their removal become very obvious. The rabbit varies in the amount of phagocytosis present in apparently normal animals and it is of interest that this method of blood destruction does not seem to depend for its stimulus upon the offering of more material to be phagocytized.

B. Fragmentation

Many facts combine to enforce the idea that red cells do not hemolyze while circulating. The toxic phenomena which accompany liberation of hemglobin in the circulation are, as has been said, evidence that disintegration must be extra-circulatory or must be accomplished without hemolysis in the sense of freeing hemoglobin and red-cell stroma in the blood stream. Furthermore, when red cells from any specimen are tested with hemolytic or hypotonic solutions, we do not find groups of resistant and non-resistant cells from the same blood. Young and old must be present but as long as they remain in the circulation they remain very much alike and we have no means in such tests of detecting old or defective cells. Rous and Robertson[164] making use of a special method, have searched "the body, organ by organ, and the circulating blood also, for disintegrating red corpuscles. Shadows of red cells are not present anywhere, nor are hemolyzing red cells found. A hemolytic process, in the ordinary sense of the term, can scarcely play an important part in normal blood destruction. Instead, it is certain that some red corpuscles, at least, are destroyed in another way; namely, by fragmentation. Normal blood regularly contains small numbers of fragmentation forms—microcytes and poikilocytes—and accumulations of them are regularly present in the spleen, but are found only inconstantly in the other organs. The fragments are in evident process of further subdivision. They occur not only in species in which phagocytosis as a means of cell destruction is negligible (cats), but also in animals in which it is an important process (dogs, some rabbits)."

The "fragmentation forms" noted by these observers seem to divide and subdivide until they reach a condition of fine dust but this entire process is unaccompanied by liberation of hemoglobin. The red cells may be thought of as breaking in pieces but not as hemolyzing. In animals receiving constant injections of blood from members of the same species and quite compatible, Rous and Robertson[164] found a great accumulation of fragmented cells in the spleen. While fragmenting cells were also found in the circulation it became evident that the spleen exercised some function towards them. Whether they break to ultimate dust in the spleen and are finally disposed of by this organ cannot be said.

In animals rendered anemic by repeated hemorrhages, microcytes and poikilocytes are often found and these cells apparently represent fragmenting cells which have been formed recently. Cells of abnormal shape are thus probably derivatives of normally shaped cells and represent stages in red-cell disintegration. Evidence for this is found in the fact that the bone-marrow of secondary anemia does not show fragmented cells when the circulating blood has been washed out of it. At the site of formation, while the red cells may vary somewhat in size, they do not show the bizarre irregularities which indicate disintegration.

Finally, and before considering the question of hemolysis, knowledge in regard to which has been largely obtained by means of *in vitro* studies, it is worth while to mention that the development of fragmented cells such as Rous and Robertson have pictured is not possible by imitation of any of the ordinary bodily conditions. Thus, prolonged shaking of blood results in hemolysis and the appearance of many shadow cells but does not cause the formation of poikilocytes nor microcytes.

C. Hemolysis

The means by which red cells retain their hemoglobin are not known. The simple observation that after escape of hemoglobin many ring-like shadow cells may be seen causes one to think of the cells as minute bladders filled with hemoglobin. But such a conception does not accord with the observation already discussed under "fragmentation", in which we have pointed out that the red cells may disintegrate down to fine dust without hemoglobin loss. Furthermore, micro-dissection of red cells shows that they may be torn in pieces without hemoglobin loss. Red-cell stroma and hemoglobin are, therefore, bound together in some manner not understood at the present time. This union must eventually be destroyed, but it would seem that its rupture and the final breakdown of hemoglobin occur under circumstances which permit exposure of very few body cells to the resulting toxic products. In speaking of leucopenia, the great rapidity with which bacilli leave the circulation and collect in certain organs has been emphasized. While direct evidence for similar accumulation of soluble proteins does not exist it is a fair assumption that it occurs and that the spleen and liver are the organs most prominently involved. In the case of normal red-cell destruction it is thus possible to conceive that cells are subdivided to rather minute dimensions but that their final rupture with the possibility of hemoglobin liberation is taken care of through the fact that fragmented cells tend to accumulate in the spleen where, if they gradually free hemoglobin, it must pass directly to the liver and in this organ leave the circulation for final breakdown to simpler products. The further fact that bile pigment can be formed from hemoglobin by other than liver cells[166] adds the possibility of constant low-grade transformation of disintegrated red cells in many parts of the body without confinement to the liver, as we have previously thought essential.

In spite of the fact that lysis of red cells is not permitted to take place in the circulation under normal conditions, it does take place in a variety of diseases and under the influence of poorly ordered therapeutic measures such as transfusions from badly selected donors. The knowledge which we possess in regard to such instances of hemolysis has arisen largely through laboratory studies of varied type and it is instructive to list some of the results so obtained.

Hemolysis as a Result of Simple Physical and Chemical Agents.—If the red cells are subjected to the influence of hypotonic solutions of sodium chloride, hemoglobin begins to leave the cells and tinge the surrounding fluid at concentrations of about 0.42 per cent. sodium chloride, and complete loss of hemoglobin will be found when a concentration of 0.28 per cent. sodium chloride is reached. This method of testing the fragility of red corpuscles has been mentioned (p. 519), and the fact that in the case of congenital hemolytic jaundice the erythrocytes hemolyze more readily has been commented upon by Minot (Vol. II, Chap. XVI). If the corpuscles which are being subjected to such a test are watched microscopically they will be seen to increase slightly in size, and eventually the observer will realize that more and more of the corpuscles are becoming shadow forms. Eventually these, too, will disappear and a clear solution of hemoglobin results. If, however, this solution is centrifugalized very vigorously, granular debris will be collected at the bottom of the tube which evidently represents red-cell stroma. Sellards and Minot[167] in a limited number of cases have shown that human beings may be given fairly large doses of a carefully prepared hemoglobin solution without untoward effects. It may be inferred from the work of these authors that the toxic symptoms incident upon intravascular hemolysis or following injections of whole laked blood are referable to the cell stroma.

In vivo hemolysis due to reduction of osmotic pressure represents a type of accident to which human beings are not subjected. Indeed, from the point of view of hemolysis, there is no need to add sodium chloride to solutions for intravenous injections since inordinate amounts of distilled water must be added to the circulation before intravascular laking occurs. The action of salts upon the red corpuscles is not limited by the question of osmotic pressure alone. Ammonium salts are thus extremely hemolytic and act without reference to the osmotic pressure. Finally, there is a possibility that certain salts such as sodium citrate, which is used very freely in blood transfusion, may alter corpuscles subjected to it so that slight grades of hemolysis occur when the blood in question is introduced into the body[168]. We have no direct evidence for such an effect but it seems a possible factor in the frequent reactions which follow transfusion with citrated blood and which are not reduced by using concentrations of citrate isotonic with the blood-plasma. Another simple influence resulting in hemolysis is rapid freezing and thawing of erythrocytes or raising their temperature above 64° C. In the condition known as paroxysmal hemoglobinuria the corpuscles may show normal resistance to hypotonic salt solutions([169, 47]) and no particular susceptibility to changes of temperature in themselves. The disease seems to depend on the presence of an autohemolysin in the serum of the patient which at low temperatures combines with his corpuscles and makes them susceptible to the action of complement. Such action is quite different from the ordinary effects of heat and cold.

Hemolysis as a Result of the Action of Lipoidal Solvents.—The stroma of the red cells contains lecithin and cholesterol, and owing to the solubility of these substances in ether, chloroform, bile salts, etc., we have in such solvents very active hemolytic agents. Efforts, however, to find diseases in which the red cells are distinguished by increased or decreased susceptibility to hemolysis by such agents have not been successful. In the case of saponin, a powerful hemolytic substance, the lipoids of the erythrocytes seem to be removed by combination with the saponin. This fact is at least true in the case of cholesterol, since saponin hemolysis can be prevented by adding cholesterol in excess.

Hemolysis Resulting from the Action of Animal and Bacterial Poisons.—The venoms of many snakes are of interest in that their action on erythrocytes resembles serum hemolysis. Thus, cobra venom will not act upon thoroughly washed red cells unless lecithin or blood-serum is added to the mixture. The venom thus resembles amboceptor. Venom hemolysis has been used to identify late syphilis[170] but is of little practical value.

In the case of many micro-organisms, substances can be extracted which are hemolytic. It is, of course, possible that such lysins account for the blood destruction seen in infections with such organisms, but direct evidence for this fact is not easy to obtain.

Hemolysis as a Result of Serum Action.—Serum hemolysis, while of vast importance for medical diagnosis, is not of direct importance in relation to the pathology of red-cell formation and destruction except in the case of paroxysmal hemoglobinuria which we have mentioned (p. 571), and in connection with the selection of donors for blood transfusion. For a discussion of this latter operation, the reader is referred to the section by Minot (Vol. II, Chap. XVI).

D. Rate of Destruction of Erythrocytes and the Final Breakdown of Hemoglobin

Many efforts have been made to determine the length of life of the individual red cells, and a variety of figures have been the result. Addis[171] estimates that 7 per cent. of the total red cells of the body disintegrate daily and that each individual cell lives for about fourteen days. Ashby[172], in studies upon the fate of transfused erythrocytes in man, comes to the conclusion that such cells live thirty days or more. The method used by Ashby is ingenious and depends upon utilization of normal blood grouping discussed by Minot (Vol. II, Chap. XVI). A patient placed in Group II is given a transfusion of Group IV cells which are not agglutinated by the serum of any of the four groups. Specimens of the patient's blood are now treated with a serum which will agglutinate Group II corpuscles. If this is done daily and the number of unagglutinated corpuscles—those from Group IV which have been introduced in the transfusion—counted, a record gradually develops which indicates the length of survival of the Group IV cells. Since these latter cells are apparently not abnormal to any individual, their length of life may well be taken to represent the length of life of the red cells.

That the normal process of red-cell destruction is so ordered as to prevent escape of hemoglobin into the circulation has been pointed out, and it is evident that there is at present a missing link in the chain of erythrocytic breakdown. Finely fragmented cells may be found in such sites as the spleen, and it is clear that both in the case of bile and urobilin we have materials to the composition of which hemoglobin is a large contributor, but the manner in which the dust-like particles of red cells are started upon the path, the end results of which are estimated in terms of pigment excretion, is not well known.

Hemoglobin is a compound of an iron-containing group and a protein group, globin. Addis[171] believes that hemoglobin is separated by the liver-cells into a pigment, hemochromogen and globin. By removal of the iron the pigment moiety is converted into bilirubin and excreted into the intestine where, through reduction, urobilinogen is formed. This compound, Addis believes, may be reabsorbed and polymerized to urobilin and eventually again become part of the hemoglobin molecule or it may be excreted in the feces and urine. In both of these latter instances the action of oxygen results, soon after passage, in the formation of urobilin. It must be understood that this view of hemoglobin metabolism represents no more than a useful working hypothesis. We have already commented upon the fact that the Kupffer cells of the liver may often be observed to contain hemoglobin. If red-cell destruction has been very intense these phagocytic endothelial cells may appear greenish and it is a fair inference that the pigment contained is biliverdin, an oxidation product of bilirubin. These facts point to the possibility that other elements than the liver-cells themselves may be able to form bile pigments, a view which is confirmed by the experiments of Whipple and Hooper[166], who have shown that hemoglobin obtained from red cells, hemolyzed by the addition of distilled water and injected into dogs, is transformed, at least in part, to bile pigment when the liver has been completely isolated from the circulation. Such transformation occurs in animals whose circulation is confined to the head and thorax alone. These authors again suggest that endothelial cells bring about the transformation they have noted. That the spleen is not essential to bile pigment formation is also evident from these experiments. It may, therefore, be held that free hemoglobin is promptly withdrawn from the circulation by endothelial cells in many parts of the body and that these cells have power to convert it to bile pigment. Under normal conditions this process takes place chiefly in the liver. It is probable that the observations of Whipple and Hooper[166] account for the findings in cases of icterus which present no evidence of hindrance to bile flow and which have been spoken of as instances of hematogenous jaundice. In chronic hemolytic jaundice, the disease which is preeminently distinguished by diminished resistance of the blood-cells to hypotonic salt solutions, it has been calculated that the individual red cells do not live more than two days. Under such circumstances we may think of bile pigment formation throughout the body with excretion into the blood stream and eventual appearance in the urine.

Whipple and his associates[173] have studied the excretion of bile pigment in animals upon different diets. They have shown that this excretion is markedly increased on a carbohydrate diet. It is hard to correlate this fact with the prevalent idea that bile pigments are formed from hemoglobin breakdown alone. Such a diet has no power to increase red-cell destruction and we are thus led to believe that other factors may enter pigment formation, a matter of importance in relation to the problems of blood destruction since some of our most important methods for gauging destruction rest upon estimations of pigment excretion. Finally it should be pointed out that, while some method for the retention in the organism of bile pigments for use in hemoglobin formation might be of great importance and economy to the body, no safe direct evidence as yet exists for such an assumption. In the case of Addis'[171] conception it is imperative that urobilinogen be absorbed from the intestine and carried again to the liver. There are, however, no recorded tests showing urobilinogen in the portal blood. We know of it as an excreted substance readily detected in feces and urine, but we fail, as yet, in direct efforts to implicate it in the formation of hemoglobin. These are points which do not necessarily negative the hypothesis of Addis[171] but which show the need for further work upon the subject.

Whatever may be the normal course of hemoglobin destruction and synthesis it is a fact that introduction of free hemoglobin into the circulation increases the excretion of bile pigment and this fact makes studies of pigmentary excretion most useful in the blood diseases.

E. Evidences of Destruction of the Erythrocytes

Blood Picture.—The observations of Rous and Robertson[164] upon fragmentation in the normal course of erythrocyte destruction make it evident that irregular and particularly small irregular erythrocytes represent cells on their way to destruction. Microcytes with regular margins may be adult erythrocytes which have developed abnormally. Irregular cells of all sizes are, however, suspicious, and if numerous, may be taken as evidence of a tendency toward blood destruction. The presence of naked red-cell nuclei and fragments of megacaryocytes are further evidence in the same direction.

Jaundice.—Blood destruction must be quite severe in order to cause any distinctive tinting of the skin unless definite biliary obstruction is present at the same time. There has been grave doubt whether a pure hematogenous jaundice could exist, it being held that in the presence of exceedingly active blood destruction the bile capillaries become plugged, whereupon jaundice results just as readily as in common duct obstruction. While such a process may accompany severe blood destruction, the observations of Whipple and Hooper[166] on bile pigment formation outside the liver render it necessary to admit the possibility of a purely hematogenous jaundice. The skin and mucous membranes in such jaundice do not reach the extremes of color found in cases of true biliary obstruction. Minot (Vol. II, Chap. XVI) has mentioned a useful method of gauging the severity of such cases, namely, through the degree of color in the serum. Many cases which show inconspicuous tinting of the skin will display a surprisingly yellow serum and the hemolytic element can thus be identified.

Fever.—Abnormal hemolysis is rarely unaccompanied by fever. If the process is steady the temperature will fluctuate as in the case of sepsis and septic infection of some sort is commonly suspected. Sudden intravascular hemolysis is usually followed within an hour by a chill, and an abrupt rise in temperature. These findings are exactly similar to those which accompany injections of laked red cells and there is some basis for believing them due to the red-cell stroma[174]. In case hemolysis is the result of injection of incompatible red cells, it is often preceded by alarming respiratory symptoms with cyanosis. These are referable to corpuscular agglutination which will be followed by hemolysis and which causes embarrassment by forming small pulmonary emboli. If hemolysis is at all protracted the spleen eventually enlarges.

Pigment Excretion.—If hemolysis is sudden and extensive, hemoglobin is found in the urine. Sellards and Minot[167] have shown that hemoglobin, injected into the circulation of patients who give evidence of increased blood destruction, appears more readily in the urine than in the case of normal individuals. Pearce, Austin and Eisenbrey[175] have suggested that when hemolysis is active the liver may become so charged with hemoglobin as to leave a higher concentration in the blood, which is accordingly removed by the kidneys.

In the normal course of blood destruction and in pathological increases in destruction, hemoglobinuria is commonly absent and, as we have pointed out, this arises from the fact that the final stages of erythrocytic breakdown in which hemoglobin liberation would occur are probably intracellular. It is, therefore, necessary to pass on to the products of hemoglobin disintegration in order to gain information upon red-cell destruction. When the bile is poured into the intestine it is converted into urobilinogen and urobilin. A fraction of these derivatives of hemoglobin is passed out with the feces and, if we accept current views, a fraction is reabsorbed to be converted back into hemoglobin in the liver. A part of this reabsorbed material is thought to account for the urobilinogen which is excreted in the urine. It is at once apparent that judgments of red-cell destruction based upon quantitations of these pigments are open to many errors, but in spite of this they are useful and at times present surprising information as to the condition of the patient. As the methods involved in urobilinogen and urobilin estimation are somewhat complicated they are given in detail as presented by Wilbur and Addis in the *Archives of Internal Medicine*, 1914, XIII, 235.*

Methods of Estimating Urobilinogen and Urobilin in Urine.—The method of collection of the twenty-four-hour urine has a considerable effect on the total spectroscopic reading. The vessel in which the urine is collected should be of dark brown glass and should be kept in darkness. Thymol crystals should be added, for even in cases in which no obvious fermentation had occurred we sometimes found a diminution in the total amount if no preservative was present. After measuring the amount of the twenty-four-hour urine, 10 c.c. are mixed with 10 c.c. of a saturated alcoholic solution of zinc acetate, and after a few minutes filtered. If a number of urines are being examined at the same time it is convenient to have test-tubes graduated to 10 and 20 c.c. Ten c.c. of the filtrate are taken and 1 c.c. of Ehrlich's solution† is added. It was found that this amount produced a sufficient concentration of acid in the mixture to give the maximum intensity of the urobilin band and contained enough of the paradimethylamidobenzaldehyd for the reaction with urobilinogen. The development of urobilinogen band is not instantaneous. We found that as a rule it had attained its full intensity in a quarter of an hour. The action can be greatly accelerated by heating, but this is to be avoided. It is better to wait for an hour before making the reading, and during this time the solution should be kept in the dark. After three or four hours there is a diminution of the urobilin and urobilinogen in filtrates from urines, so the estimation should be made not later than three hours after adding the Ehrlich solution. We found that Citron's hand spectroscope was the most convenient instrument to use. The filtrate was washed into a graduate and diluted with tap-water until first one and then the other bands of light absorption had disappeared when the full amount of light entered the spectroscope, but were still visible when the light was partly shut off. This gives a fairly definite end-point, and we did not find any great variation in the readings made by different persons. It is important of course that the light shall be always of approximately equal intensity. We made the readings in a dark room with a Tungsten electric bulb, holding the spectroscope close to the source of light. In highly colored urines one may be in doubt as to whether or not a trace of urobilin is present, for there may be so much general absorption of light as to obscure the urobilin band in the undiluted filtrate. There is no such difficulty with the urobilinogen band which lies between the red and yellow where there is no marked light absorption. With urines containing bile, if the amount of urobilin is not very large, it is necessary to add some Fuller's earth and to leave the mixture standing for some time before filtration. If this is done the urobilin band can usually be read even in the undiluted filtrate. The dilution required gives the value for 5 c.c. of urine. If this figure is multiplied by the number of 5 c.c. quantities in the twenty-four-hour urine, the number of dilutions which would have been necessary if all the urobilinogen and urobilin in the twenty-four-hour amount had been concentrated in a volume of 5 c.c. is obtained. For instance, if in a twenty-four-hour urine measuring 1,000 c.c. readings of ten dilutions for urobilinogen and of twenty for urobilin were made, the total urobilin would be 30 x 200 = 6,000. We tried to determine the dilution value of definite weights of urobilin prepared from bilirubin, but different preparations varied so much in their dilution value that it was obvious that we were not dealing with pure urobilin and we abandoned any attempt to express our results in milligrams of urobilin.

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* Recently Boyd[176] has modified these methods by a convenient improvement in the spectroscope.

† "Paradimethylamidobenzaldehyd, 20 gm.; concentrated hydrochloric acid, 150 c.c. water, 150 c.c."

Methods of Estimating Urobilinogen and Urobilin in Stools.—"All the feces passed in the twenty-four hours were collected in the same receiver, the stools being protected from light. They were then washed into a large graduate and thoroughly ground up with water into a homogeneous paste, and water added to 0.5, 1, or if necessary 2 liters, depending on the quantity, was added. The mixture was then put into a shaker for about half an hour. A considerable number of extractives were tried for removing the urobilin from the stools, but none was found so efficient as alcohol with hydrochloric acid (95 per cent. alcohol, 1,600 c.c.; concentrated hydrochloric acid, 25 c.c., and water, 800 c.c.). After thorough mixing in the shaker an equal quantity of a saturated solution of zinc acetate in alcohol was added and the mixture was filtered. After adding 2 c.c. of Ehrlich's reagent to 20 c.c. of the filtrate, the solution was put aside in a dark place until next day. The addition of zinc acetate is not absolutely essential, but in some cases we observed an intensification of the urobilin band following its use, and it is perhaps an advantage to make the urine and stool readings as far as possible under the same conditions. The development of the urobilinogen band was not always complete until six hours had elapsed, but thereafter there was no loss of urobilinogen or urobilin for a long time, although this was not the case with the zinc acetate filtrates before the addition of Ehrlich's solution. The reading was made in the same way as with the urine and the total amount calculated for the volume of stool after grinding up with water, the dilution of the 25 c.c. by acid alcohol and zinc acetate being taken into account. Instead of using tap-water for dilution of the final extract, 60 per cent. alcohol was required to avoid the development of a precipitate."

In order to get a more perfect estimate of the amounts of urobilinogen and urobilin in the intestine, Schneider[177] studied the duodenal contents for these substances, removing the material with Einhorn's duodenal tube and estimating bilirubin by means of Huppert's test, and urobilinogen and urobilin through the methods of Wilbur and Addis. Giffin, Stanford, and Szlapka[178] have made the same observations and agree with Schneider in believing that the duodenal contents may present valuable information upon increase in blood destruction. Hansmann and Howard[179] more recently disagree with these opinions and conclude that, "The evidence of abnormal hemolysis occurs first in the stools, second in the duodenal contents, and lastly in the urine."

Pigmentary Deposition.—Increased blood-cell destruction will cause deposits of pigment some of which contain iron and some of which do not. The liver, spleen, bone-marrow and kidney are the most frequent sites for such deposition.

Destruction of the Granular Leucocytes

The fate of the leucocytes under normal conditions is unknown. They are cells whose function of phagocytosis is practically carried out in the tissues. We examine them in smears from the circulating blood when they are perhaps on the way to functionate or else they are studied in exudates and sections of lesions in which they are actively at work. It is probable that a certain number of leucocytes are steadily lost by wandering into the lumen of the intestinal tract and many pass out each day upon the mucous membranes of the respiratory passages and eventually disintegrate. The high protease content of the leucocytes causes autolysis with great readiness and probably represents the final step in disposal of them.

Dickson[16] has studied the degenerative changes in the granular leucocytes of the bone-marrow under a variety of conditions. The nuclear changes which occur consist of a preliminary condensation of the nucleus (pyknosis) followed by fragmentation of the nucleus and gradual disappearance of the nuclear particles in the cytoplasm or karyolysis characterized by swelling of the nucleus and solution of its chromatin. This last process of nuclear lysis is occasionally preceded by pyknosis but is more frequently without it. Pyknosis of leucocytic nuclei is quite common in the circulating blood of the dog and we have seen it well marked in one human case. The cells in question in this instance were mistaken for peculiarly large basophilic nucleated red cells. The fact that degenerative nuclear changes are ordinarily accompanied by a loss of typical cytoplasmic granulation makes it easy to fall into such a mistake. The loss of granulation is usually accompanied by vacuolation until the entire cell-body becomes a poorly staining shred-like network and disappears. We have no knowledge whether myelocytes are more or less resistant to degenerative influences than are adult leucocytes.

Close observation of the blood, when leucocytosis is high, will usually reveal a few cells showing degenerative changes such as we have described, but in the main they occur in or about the site of infection and when seen in the circulating blood have little clinical significance.

In myelogenous leukemia one regularly finds leucocytes showing loss of granulation, vacuolation, and all forms of shredding distortion of cytoplasm. Ordway (Vol. II, Chap. XVII) has pictured such degenerated cells. The autolytic enzymes of the leucocytes are normally rendered powerless by anti-enzymes in the blood, a situation which does not seem to exist in leukemia[180]. As a consequence proteases are frequently found in the blood of such patients[181] and products of the decomposition of nucleoproteins in the urine[182]. In regard to this last feature of leukemia, which is expressed by increase in uric acid, the purine bases and phosphoric acid, results have differed rather markedly, but such a circumstance is not surprising when one considers the fluctuant character of the disease. Owing to the fact that lymphocytes are less prone to autolyse than the leucocytes, one would expect to find less evidence of degeneration through urine examination in lymphatic leukemia, and such is the fact.

Finally, certain substances have been found which are notably destructive to the leucocytes. Perhaps the most noticeable of these is benzol[183] which, in small doses, is almost specific as a leucotoxin. Radium emanations and X-rays cause leucocytic destruction and are consequently of the greatest use in the treatment of leukemia. They, however, do not exhibit such great specificity as is seen in the case of benzol.

Destruction of the Endothelial Leucocytes

The fate of these wandering cells is no doubt lysis in the tissues in the neighborhood of toxic foci which have attracted them, but nothing definite can be presented in regard to them.

Destruction of Megacaryocytes and Blood-Platelets

Any agent bringing about red-cell destruction operates against the platelets and megacaryocytes. Thus, Duke[184] found the platelets much reduced in the late stages of benzol poisoning when anemia becomes prominent. While the platelets ordinarily vary in number in proportion to the vigor of red-cell formation at the moment of examination they may be greatly reduced, independent of red-cell change—the noteworthy finding in certain purpuras as has been pointed out by Minot (Vol. II, Chap. XVI). What the destructive process is in such cases, we do not know. The fact that Lee and Robertson[185] by repeated injections of guinea pig platelets into rabbits have succeeded in producing serum which would destroy the platelets of the guinea pig with consequent purpura is of interest in this relation.

The normal disintegration of the platelets seems to occur when vascular rupture causes them to pass beyond the endothelial lining of the vessels. Under such circumstances they apparently exercise their true function, disintegration and liberation of prothrombin and thromboplastin. Prior to disintegration, they tend to stick to one another and to practically any tissue with which they come in contact. Wright and Minot[186] have recently described this viscous metamorphosis of the platelets and its relation to blood coagulation.

Destruction of the Lymphocytes

As in the case of the leucocytes the normal fate of these cells is unknown. Certain agents such as the X-rays and radium emanations are peculiarly destructive to them. Murphy[83] has shown that lymphoid tissue may practically be eliminated by X-ray action and has also brought out the fact that actinic rays and dry heat[161] induce marked lymphocytic degeneration. If we except, however, these special agents, we find that the lymphocytes are very resistant to toxic agents. Studies upon the protein metabolism in lymphatic leukemia give no such marked evidence of cellular breakdown as is attained in myelogenous leukemia, a fact which apparently is referable to the low content of proteolytic enzymes in these cells.

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CHAPTER XVI

DISEASES OF THE BLOOD (*Continued*)

CLINICAL DISCUSSION OF THE ANEMIAS

By GEORGE R. MINOT

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Introduction

Pallor alone does not mean anemia. Individuals may look pale who do not have reduction of their hemoglobin available for carrying an oxygen supply sufficient for the needs of the body, and in whom the amount of hemoblogin per unit of blood is not less than normal or in whom the red count is not reduced. Constriction of the peripheral vessels, as in fainting, or increases of fluid in the tissues, as in nephritis, are instances when pallor may occur without anemia. It should also be noted that individuals may thoughout life appear pale and not exhibit anemia. Pallor is of course a feature of anemia and an icteric tint is associated with the hemolytic forms, but an icteric tint is not always present in such cases. However, individuals with the lesser grades of anemia, and even with some of the more marked grades, may not appear pale, because of concentration of their blood mass or dilatation of their peripheral vessels, or because the natural or abnormal tint of their skin, pigmentation, jaundice, etc. may obscure the pallor. Besides pallor, there are certain symptoms and signs that may occur with an anemia from any cause, dependent directly or indirectly on the anemia and insufficient supply of oxygen to the tissues, and varying with the character, duration and intensity of the anemia. These are as follows: headache; vertigo; faintness; general muscular weakness and abnormal fatigue; increased sensitiveness to cold; irritability; lack of power of concentration; slight disturbance of sight, as black spots before eyes; tinnitus; palpitation with increased pulse rate; simple systolic murmurs, also evidence of a weakened myocardium; venous hums; low blood pressure; dyspnea; shallow breathing; slight elevations of temperature; simple gastrointestinal disturbances, as nausea, lack of appetite, constipation, and at times diarrhea and vomiting; slight traces of albumin in the urine and low specific gravity; amenotrhea; and edema. The latter is probably associated with hydremia, absolute or relative, and is also associated with a deficient myocardium due to the anemia. It is important to remember that such symptoms and signs may be dependent upon anemia, so that other conditions with similar symptoms may not be wrongly diagnosed as anemia.

Individuals with anemia may compensate for their deficient supply of hemoglobin by either an increased blood flow or by the tissues taking out more oxygen from the blood, leaving the venous blood less saturated with oxygen than normal. Such topics will not be discussed in this article, though such fundamental considerations are of great importance in our understanding of the mechanism of the human body, and by the advancement of such knowledge we shall learn more about the clinical state and prognosis of our patients.

There are also many other conditions that are of great interest in relation to anemia that will not be discussed, largely because of the present imperfect knowledge of these subjects or from a lack of immediate clinical application. We refer to such subjects as anoxemia, excellently discussed by Haldane[1]; alterations in the physical and chemical character of hemoglobin; variations in the oxygen and carbon dioxide content of the venous and arterial blood in relation to the clinical state of the patient; changes in the sizes of the red cells with and without alteration in their hemoglobin content; chemical changes in the cells and plasma; metabolic changes in different types of anemia; effects of anemia on immunity, etc., etc.

The anemias will be discussed in the following order, first, those due to blood loss, next, those due to particularly defective blood formation, and then those associated with distinctly increased blood destruction.

Anemia Due to Blood Loss

Drinker (Chap. XV) has fully discussed the effect of hemorrhage on the blood forming tissues; the reader is referred to that chapter for a consideration of this subject. Thus no particular description or further discussion will be given here on the rate of regeneration of blood following blood loss, the effect of hemorrhage on the marrow and its elements in the peripheral blood, or its effect on blood volume, coagulation time, etc. The various surgical aspects of hemorrhage will not be discussed, such as the local symptoms or signs produced by hemorrhage and the differential diagnosis of hemorrhage from other surgical conditions, as peritonitis.

(1) Acute Anemia Due to Blood Loss

The symptoms produced by an acute anemia due to blood loss are fully as much dependent upon the rate at which the blood is lost as upon the amount that is lost, because reduction of blood volume, as discussed by Drinker, is an important feature in this condition. Any of the symptoms and signs common to anemia may occur; but with acute hemorrhage and considerable blood loss, increased pulse rate, sweating, restlessness, and rapid, shallow breathing owing to insufficient blood supply to the tissues, will be features. As the blood volume returns to normal, the severity of the symptoms cease and the patient while at rest is comfortable, though mild symptoms from the anemia will persist until the blood is regenerated.

The hemoglobin percentage and red cell count following hemorrhage at first may not appear abnormal, due to total reduction of the blood mass, and so one cannot estimate the amount of blood lost by these determinations. As the blood volume is restored reduction in the percentage of hemoglobin will be found to be relatively greater than reduction in the red cell count. Hence a low color index will be observed and the red cells will appear achromic. The achromia will increase in the earlier period following the blood loss, because the red cell increase occurs proportionally faster than the increase of hemoglobin. The blood picture of acute post-hemorrhagic anemia will of course vary in degree dependent on the patient's condition, and the rate and the amount of blood lost; but it is essentially characterized by evidences of rapidly increased activity of all the marrow elements. These evidences are, increases of bone marrow white cells, the white count often reaching 15,000; increases of platelets, their count often reaching a million; and increases of young red cells, the reticulated cells often reaching ten per cent. The red cells, besides showing achromia and evidence of youth (reticulation, polychromatophilia, nucleated cells) will show an abnormal but not marked variation in size, their average size being smaller than normal, though true microcytes are not seen. Variation in shape of a relatively slight degree may occur. This type of acute anemia is the one that most frequently causes a very marked increase of platelets, and these platelets average small in size.

As the days pass following hemorrhage, the degree of activity of the marrow lessens and so the number of young red cells and other bone marrow cells in the peripheral blood gradually decreases, as Drinker has described. It is noteworthy, however, from the aspect of diagnosis, that if one believes a hemorrhage from a concealed source is recurring, further evidence of this may be obtained from the blood picture, because, following the rise of reticulated cells after hemorrhage, they progressively diminish, if the hemorrhage has ceased, while if hemorrhage persists, they may increase or at least not become fewer.

There is seldom opportunity to confuse anemia due to acute blood loss with any other type of anemia because evidence of the hemorrhage itself should be easily obtained. The remarks that follow serve to indicate the confusions that might arise and apply not only to anemia from acute blood loss but also to anemia from chronic hemorrhage. When hemorrhage occurs from injury or disease of the different organs of the body, the response of the marrow will vary greatly according to its state. For example, if hemorrhage occurs in an individual who already has a simple chronic anemia from sepsis or malignancy, the response of the marrow will not be as good as in an individual whose marrow is normal before the hemorrhage occurred. Not only may hemorrhage be an added cause of anemia in a patient with a simple chronic anemia, but it may be an added cause in other anemias, as from bleeding hemorrhoids in a patient with pernicious anemia. In such an instance the blood picture of pernicious anemia remains, though the hemorrhage may cause some temporary increase of the bone marrow elements and young red cells above their previous level. This change, however, is nothing like so marked as when the marrow is normal prior to the hemorrhage. Likewise in Banti's disease, with its depressed marrow activity, hemorrhage from ruptured esophageal varices will not cause the same degree of marrow response as is seen in normal people following traumatic hemorrhage. Thus one must remember that an acute anemia due to hemorrhage may be engrafted upon some other form of anemia. This partially explains why patients regenerate their blood following hemorrhage at different rates and in very different degrees.

It is to be noted that hemorrhage, besides resulting from injury and disease of the different organs, may occur as a symptom dependent upon blood defect, particularly in cases with primary blood disease. When such is the case we will find the blood of a different character than when acute anemia from blood loss occurs in an individual with no such defect. Not only hemorrhage, but the ensuing anemia, which occurs in idiopathic purpura hemorrhagica, can be distinguished from that resulting from a local cause by the blood picture, among other things, because with purpura hemorrhagica the blood platelets are markedly diminished while following simple direct hemorrhage they will be markedly increased. In both conditions the character of the red cells is the same with increases of young red cells. The bone marrow white cells also increase in both conditions, though not uncommonly they will be proportionally more increased following simple direct hemorrhage in a normal individual than in idiopathic purpura hemorrhagica. An entirely similar blood picture occurs when purpura hemorrhagica is secondary to some other disease, as diphtheria, and when secondary to some blood disease, as pernicious anemia or leukemia; except that then the picture of the blood disease will also be present and the response of the white cell and red cell elements will depend upon the functional state of the marrow in these conditions. The histological blood picture following hemorrhage in hemophilia is entirely similar in all respects to that following direct hemorrhage with a healthy marrow. This is because in hemophilia the ability of the giant cells of the marrow to produce platelets is not altered, though their physiological character is abnormal. However, in hemophilia the coagulation time of the blood will be distinctly prolonged, while with simple direct hemorrhage it will be shortened.

(2) Chronic Anemia Due to Loss of Blood

The commonest causes of repeated blood loss that produce a chronic anemia, are hemorrhoids, uterine disease, hepatic cirrhosis and peptic ulcer. There are no symptoms or signs particularly characteristic of such an anemia.

Drinker (Chap. XV) has discussed already the character of the bone marrow and of the blood following repeated hemorrhage and how the response of the marrow will vary, dependent upon the duration, frequency and amount of repeated blood loss. We must remember that the marrow responds less and less and recovery will occur more slowly, the more repeated and constant the blood loss and the poorer the state of the patient. Loss of blood, continued for years, may injure the marrow so that it is very difficult or perhaps impossible for the individual's blood to return to its absolutely normal condition.

The blood picture from chronic blood loss may be summarized by saying that it is essentially like that observed with acute anemia due to blood loss, except that the findings indicate a less degree of marrow activity, though the degree of activity will be of course relatively greater following each hemorrhage than between hemorrhages. Hence, between hemorrhages, the usual blood findings are a moderate, not often very marked, increase of platelets and bone marrow white cells, while occasionally with marked depression of the marrow a leucopenia may occur. Only a few young red cells will be seen. Variation in size of the red cells occurs usually to a greater degree than is seen resulting from one or two hemorrhages. The average size is small though macrocytes may be found, while microcytes resulting from defective formation rather rarely occur. Variations in shape, like variations in size, are more marked than with acute anemia following blood loss, so that cells apparently poorly formed are commonly seen. Achromia and a low color index occur.

The diagnosis of this type of anemia depends on obtaining a history of chronic hemorrhage or upon finding a cause for bleeding. The blood picture is not distinctive. It is the same as occurs in many cases of chronic simple anemia from various causes, and some anemias due to blood loss may have a blood picture resembling chlorosis. Repeated blood loss may be a symptom of a blood defect and may be an additional cause of anemia in an individual with some other form of anemia, which in turn may be the cause of a poor response of the marrow to the blood loss, as has been referred to under acute posthemorrhagic anemia. In fact, it is more often with repeated rather than with acute blood loss that confusion may be caused with the conditions previously referred to. To emphasize this point the following example is given. The anemia of chronic, acquired or congenital purpura hemorrhagica is due to repeated blood loss and this may be from one particular part of the body. It is, however, most important to distinguish the various forms of purpura hemorrhagica from bleeding due to local causes. Among other methods, as previously stated, this may be done by the fact that the platelets are very scant in purpura hemorrhagica, while if the bleeding is from a local cause, they are increased. Among the examples where anemia due to repeated blood loss might be considered the wholly correct diagnosis when such is not the case, the following is cited. Simple chronic anemia due to intestinal parasites may be complicated by some blood loss. If the parasites are overlooked one might be led to believe that the blood loss accounted for all the anemia present, when the greater part of the anemia really was dependent upon the parasites.

Chronic anemia due to blood loss has at times been confused with pernicious anemia not only because cases with chronic hemorrhage may have relapses and remissions, dependent on the presence or absence of recurring hemorrhages, but also because chronic hemorrhage from hemorrhoids is not a rare complication of pernicious anemia. Likewise, in some cases of long standing chronic anemia from repeated hemorrhage some real macrocytes, not a general macrocytosis, may occur, and the color index may be but little reduced, and this may be combined with evidence of depressed activity of the marrow. In contrast to pernicious anemia there is no blood destruction in anemia due to blood loss. It is true, as early pointed out by Stockman[2], that it would seem as if chronic hemorrhage might be the starting point of certain cases of pernicious anemia, but the typical histological blood findings of pernicious anemia, combined with increased red cell destruction, can not be reproduced by chronic hemorrhage. In these cases, where chronic hemorrhage appears to be the starting point of pernicious anemia, it seems that they are comparable to instances of cancer of the tongue which have been inaugurated by irritation. Not that the irritation is the direct cause of cancer, but that it placed the tissues in a state which permitted cancer to develop. Similarly, chronic hemorrhage in individuals perhaps with a susceptible hematopoietic tissue may permit in some manner the onset of the pathological condition known as pernicious anemia. Many instances reported as pernicious anemia due to chronic hemorrhage have been shown by autopsy not to have been pernicious anemia; the diagnosis was incorrect because of lack of proper scrutiny of the blood.

ANEMIA PARTICULARLY DEPENDENT OR WHOLLY DEPENDENT ON DEFECTIVE BLOOD FORMATION

(1) SIMPLE CHRONIC ANEMIA ASSOCIATED WITH DEFECTIVE BLOOD FORMATION

The conditions that may cause a simple chronic anemia, are practically as numerous as those that may affect man. Among the causes of such an anemia are infections of all types, including those with intestinal parasites, intoxications from poisons, as lead, mercury, arsenic, etc., and intoxications from diseases of the kidneys and liver, particularly cirrhosis. Many chronic diseases, particularly those of the gastrointestinal tract, both functional and organic, malignant neoplasms, disturbances of the glands of internal secretion and pregnancy are among the causes of such an anemia.

Improper food also can give rise to simple chronic anemia, though starvation alone in a healthy man, as Ash[3] and others have shown, may not affect significantly the blood. The relation of blood defect to the type and quantity of food is worthy of greater study than has been given to it. Recently[4] it has been shown that not only profound metabolic changes, but also a mild anemia, occur in normal men on simply a reduced diet. Poor hygiene, including lack of sleep, may be responsible for some cases of simple chronic anemia, and when such conditions are combined with improper food, the anemia appears to be greater than when either alone is the apparent cause.

There is one particular dietary defect that is a distinct cause of a chronic simple anemia. This defect is iron starvation, which leads to a defective formation of the blood, as Ehrlich and Lazarus[5] and Finkelstein[6] have shown. Anemia in such a case may develop upon taking a strict milk diet over too long a period owing to the small quantity of iron in the milk. This occurs especially at the end of infancy. Finkelstein[6] considers that an undeveloped hematopoietic system may play a part in some such cases.

There has been described a condition of chronic anemia with achylia gastrica and polyarthritis, which has been thought by some to be a special form of anemia. This subject has been summarized by Borries[7]. It seems that this form of anemia is dependent upon a low-grade infection and is not different from that seen with other instances of simple chronic anemia with evidence of inactivity of the marrow elements.

Simple chronic anemia is often of but a slight degree as when caused by improper foods, simple gastrointestinal disorders, early pregnancy, and chronic focal sepsis, but all degrees may occur, a severe grade as may occur with cirrhosis of the liver, malignancy, intestinal parasites, etc., being relatively less common.

Rarely is there caused by this simple form of anemia as low a level of red cells as in pernicious anemia, yet the patients appear sicker from the anemia itself at a given level of red cells or hemoglobin. It would seem in either instance that they suffer proportionally to their hemoglobin level rather than their red cell level.

Simple chronic anemia usually gives a blood picture essentially similar to that present in cases with chronic recurring blood loss between hemorrhages, and the condition is commonly referred to as chronic secondary anemia, but it is to be distinguished from an anemia which may give a similar histological picture and in which distinct evidences of red cell destruction are present.

As Drinker has pointed out, it must be recognized that all forms of anemia may occur, from that due purely to absent blood formation to that due purely to increased blood destruction, and that between these extremes occur instances where both factors play a part and where one factor may be much more in evidence than the other. These factors may, of course, act to produce anemia very rapidly or very slowly, and permit an anemia to improve in like manner, as well as to be maintained at a given level.

Distinct evidences of red cell destruction are not present in simple chronic anemia, as is well known, which is in contrast to most cases of pernicious anemia and to the hemolytic anemias. Martin[8], as well as others, by the newer methods for measuring blood destruction, has confirmed this point.

However, it is highly probable that in many of these simple anemias in which blood formation seems to be particularly adversely affected, there does occur some, but relatively slight, blood destruction. This quite possibly may occur in a different manner from that in the distinct hemolytic anemias, or occur so much more slowly that the distinct evidences of it are not seen. Though some of the anemias, considered to be of the simple chronic type, probably have some abnormal degree of blood destruction at some time in their course, or even throughout it, as in some of those associated with infections, lead poisoning, malignancy and nephritis, others are probably purely dependent upon defective formation[9], as those caused by senility, myxedema and benzol poisoning, which latter condition may progress to that of complete aplasia.

The form of anemia under discussion has been called chronic in contrast to acute anemia from hemorrhage and acute anemia dependent upon rapid blood destruction, though it is to be noted from the discussion below, that this form of anemia may develop in a short period of time. Marked anemia can develop from purely deficient or absent blood formation but it can not develop very rapidly, because red cells circulating in the body will continue to live and die at their normal rate. Destruction of the blood alone or with decreased activity of the marrow causes more rapid development of anemia. A good example of this is the anemia that often develops in a few days with acute infectious arthritis. In such an instance destruction, for a time at least, has probably been active in producing the anemia, as marrow inactivity alone would not produce such an anemia so rapidly; destruction then ceases and there occurs a sluggish regeneration so that the normal blood level is seldom reached as rapidly as when a similar amount of anemia is produced from hemorrhage. In some instances, the anemia may remain of a moderate degree for a considerable time. In contrast to this chronic anemic condition which has appeared rapidly, are those other cases of simple chronic anemia occuring with malignancy, cirrhosis of the liver, etc., which may develop very insidiously and progress slowly to a very low level.

The reason for calling this form of anemia under discussion "simple" is that apparently no radical change has taken place in the type of blood formation, such as seems to occur in true pernicious anemia. The red marrow itself commonly shows hyperplasia, but the cells resulting from this effort at increased activity would seem to enter the circulation slowly, though those that do enter may be young or very immature. It has been brought out in the previous chapter that not only the amount but the rate of marrow growth is important in regeneration of the blood. In other instances, it would appear that the cells produced are abortive or defective, not only in their structure but perhaps because hemoglobin cannot be properly synthesized, so that they do not fulfill their function properly, and quite possibly they die abnormally rapidly for some unknown reason, but not dependent upon any increased hemolytic process. At other times, the marrow may show partial, patchy atrophy or local gelatinous degeneration alone or combined with areas of hyperplasia, so that formation may be defective from lack of sufficient tissue. Such a process, if it progresses, eventually gives a complete aplasia, which will be discussed separately.

The detailed blood picture in these cases will vary of course with the degree of anemia present and the degree of response the marrow is able to make. It will vary with the different varieties of defective formation, which may or may not be associated with slight degrees of increased blood destruction, and it will vary because one element of the marrow may be more affected than another, though the red cells would appear always to be affected earliest and most markedly. Likewise variations in the picture will depend directly on the cause of the anemia itself, because the causative factor may have been a special influence on one or another of the blood elements. For example, sepsis, cancer, etc. cause leukocytosis, and typhoid fever leukopenia, while lead poisoning produces a predominance of stippled red cells whose numbers parallel more the grade of anemia than the degree of poisoning.

A feature of the blood picture in simple chronic anemia is a low color index so that achromia is evident though frequently not marked as is the case in chlorosis; this is in contrast to the high color index of pernicious anemia. Usually, besides achromia, the red cells show simply variation in size with relatively little variation in shape. The tendency is to cells slightly smaller than normal, with a few or no true microcytes due to blood destruction, though very small cells due to imperfect formation may occur. The platelets and white cells are commonly somewhat increased, rarely so markedly as in posthemorrhagic anemia. Young cells, shown by polychromatophilia, reticulation, etc., are commonly present but seldom are found in marked numbers. When their numbers are distinctly increased, particularly if the level of the anemia is not rising, one should look for evidence of loss of blood or for evidence of some agent that is persistently stimulating the marrow as products of red cell destruction, toxins or poisons, or changes in the oxygen want of the marrow.

Though variations in shape occur and microcytes may be present, such findings are seldom as evident as in pernicious anemia. When considerable degrees of either of these abnormalities occur, and particularly with tailing of the red cells, it would suggest that blood destruction was active.

In severe cases the red cell picture may be markedly abnormal, so that marked variation in size occurs, with large round cells present, but still the majority of the red cells are normal or slightly smaller than normal. With such are inevitably associated changes in shape but usually relatively less marked than the variations in size. Nucleated red cells and other evidences of a severe effort on the part of the marrow to form blood may occur; with such a picture, leukopenia and diminished platelets may be present, so that the picture may at times closely resemble that of pernicious anemia. In fact, there are certain ill-defined cases of anemia, where the color index is about one, and in which some macrocytes occur, that may be readily mistaken for pernicious anemia and are perhaps impossible to distinguish from it. Such cases, in some instances, seem to be dependent upon liver disease, and this and syphilis among other conditions are to be thought of when such a picture presents itself.

Though the cause of this simple chronic anemia in most patients is usually recognized, not uncommonly we find individuals with such an anemia of slight grade and sometimes even of marked grade, in whom we do not discover the cause; rather more commonly this is the case in women than in men. Some such cases are probably dependent upon unrecognized focal sepsis, derangements of the liver and gastrointestinal functions, and disturbances of the glands of internal secretion, while some others may be mild grades of chlorosis or dependent upon some congenital deficiency of the hematopoietic system, marked degrees of which have been reported as occurring rarely in children[10, 11]. In young infants the blood forming tissue sends forth immature cells much more easily than in adults, so that a condition causing a simple anemia may produce a more abnormal picture in an infant than in an adult. In fact the infantile hematopoietic tissue reverts readily to its embryonic condition and, as a result of this, there occur cases with extreme anemia with white pallor, where a cause for an anemia is found, and in which no evidence of hemolysis is present, but there is a histological blood picture entirely similar to pernicious anemia, with many early marrow cells of all forms. A high color index occurs and macrocytes and few platelets are present. As some such cases appear to occur without discoverable cause, the question arises, when a cause is recognized, whether the cause is wholly responsible for the anemia or whether some congenital deficiency has permitted a perverted form of defective blood formation to occur. There is a type of case in which blood formation resembles the type seen in pernicious anemia, but the disease-condition in the child does not resemble the disease pernicious anemia. Cases showing the condition referred to may well be grouped separately from simple chronic anemia, as this type of blood formation is different from that of the other conditions discussed under simple chronic anemia, but on the whole it seems clearer to include them in this discussion.

It would seem probable that some obscure cases of simple chronic anemia in others than infants, without a severe degree of anemia, may be dependent upon a primary alteration of the hematopoietic system itself. These perhaps may be somewhat similar to the rare instances of a congenital deficiency of the hematopoietic function though giving a blood picture like other cases of simple chronic anemia.

Not infrequently cases of simple chronic anemia occur, dependent upon unrecognized or ill-defined causes, which remain chronically anemic for years but which do not seem to get seriously so. The bone marrow appears to be sluggish as evidenced particularly by absence of increases of platelets or white cells, the presence of abortive forms of white cells and imperfectly formed red cells, narrow, elongated, round-ended red cells being at times a feature. In such cases it seems that the organism has found that it is so much easier to establish for its particular red cell and hemoglobin level a new one somewhat below normal, that it has persistently kept at such a level; and it would seem that in such instances it was very difficult, and sometimes impossible, to restore blood formation to a wholly normal level. An instance of this condition is as follows: We have followed for three years a patient severely poisoned by benzol, who still shows evidence of a chronic simple anemia of a low grade as determined both from observation of his blood smear and of his hemoglobin and red count; his anemia now is of a low grade quite like what he showed two and a half years ago, at which time his red count had risen to 4,000,000 from 1,000,000 after numerous transfusions. This suggests that the poison had injured the blood forming organs to such a degree that they functionated with greater satisfaction when the level of his blood was kept at about 80 per cent. of normal.

From what has been said about simple chronic anemia, particularly that associated with defective blood formation, it will be seen that the diagnosis depends upon finding a cause for the anemia and excluding the other anemias discussed in this general section.

The patients are pale, not icteric, and the symptoms are those of anemia along with symptoms resulting from whatever factor that is causing the anemia.

The prognosis depends on the cause, duration and intensity of the anemia and upon the degree of involvement of the marrow.

(2) Chlorosis

Chlorosis is a disease that occurs in women, particularly at the time of puberty or just following the establishment of menstruation. It rarely occurs after the age of twenty-five. When it does occur after this age, the individual has probably had a previous attack. The articles on this disease by Albutt[12], von Noorden[5], Cabot[13], Ward[11], Gulland and Goodall[14], and

Morawitz[15] are very complete; von Jagic[16] has discussed chlorosis more recently. The exact nature of the disease is unknown but it appears to be associated with a defective blood formation. There is no evidence of increased red cell destruction. With the defective formation there is said to be an increase in the total blood volume, the increase being particularly of the plasma. This is said to return to normal as improvement occurs. Haldane[17], Smith[18] and Plesch[19] by using the carbon monoxide method have shown that an increased blood volume was present in chlorosis. Criticisms have been advanced concerning the method and the fact has not been definitely established. The views concerning chlorosis might be distinctly clarified if the blood volume was further studied by improved methods and it is our impression that a diminished volume may occur.

Numerous theories have been advanced as to the immediate cause of chlorosis; on account of the time of onset of the disease it would seem that alteration of the internal secretions of the genital glands played some part in its causation. Changes in location, poor living conditions, improper food, all seem to play a part in the disease, as it is much more common in domestic servants than in others, though no class is immune. Predisposition seems to occur in certain families. Whatever is the cause of the condition, there is one striking fact about it, and that is that chlorosis seems to be distinctly rarer than some years ago.

The onset of chlorosis is usually gradual, over a period of three to eight months, though sometimes quite sudden; occasionally individuals may not feel well for a period of two years prior to treatment or before improvement occurs. The tendency is towards spontaneous improvement. Cabot[13] has noted "that under treatment the disease is so far relieved that the patient is able to go back to work and feel nearly, if not quite, well within six months," and commonly sooner, rarely longer. It is not unusual to find cases having more than one attack, but if properly treated relapses will rarely occur. The disease is rarely fatal, and if so the fatal issue nearly always results from thrombosis.

The symptoms are those of anémia. Weakness and breathlessness are common early, and suppression or irregularity of the menses is the rule. Certain symptoms that are particularly associated with chlorosis rather more often than with simple chronic anemia, are those referable to the gastrointestinal tract and the nervous system. Dyspepsia is common and an unusual and often perverted appetite for sweets, pickles, etc., frequently occurs, as does a neurasthenic disposition with irritability, insomnia, neuralgic pains and vasomotor disturbances.

The green color which gives the disease its name is seldom seen and only develops in a few instances where the blood changes are marked, and even then the individual's appearance is hardly green but does have a somewhat greenish hue about the eyes and chin. Pallor, however, is often striking; it is usually not the dead white color of acute hemorrhage and never the definite yellow color of hemolytic anemia, but is a yellowish white like that seen with edematous tissues.

Of physical signs, there are none peculiar to chlorosis. Fever of a slight degree may occur. The spleen in ten per cent. (Ward[11]) of the cases is a trifle enlarged. Edema is rather a feature of this form of anemia, and it is important to remember this because the clinical picture may be like that of nephritis. The edema usually affects the feet, but may appear in the hands, face and eyes. It is probably dependent upon alterations in the blood volume.

Thrombosis is the only important complication of the disease, occurring particularly in the legs, but it may occur in the cerebral sinuses. A tendency to thrombosis is well recognized, though it occurs in but about two per cent. of the cases, as stated by Cabot[13], von Noorden[5] and Gulland and Goodall[14]. The greatly increased numbers of platelets in some of these cases may be an important contributory factor to the formation of such thrombi.

Little is known about the condition of the marrow because death is so rare, but hyperplastic marrow usually has been found. Defective blood formation would seem to occur as shown by a study of the blood, and some of this defect would seem to be dependent upon a disturbance in the formation of hemoglobin in the cell. Studies on the iron metabolism have yielded very variable results[20]. The trend of opinion is that the body has enough iron but cannot utilize it, though when iron as such is given by mouth it is able to do so.

The characteristic feature of the blood is a marked reduction of the hemoglobin in each cell so that a very low (0.5) color index occurs; achromia is marked, while the red cells are usually not at all or but slightly reduced in number. It is most unusual to find the count 2,000,000, and it is usually about 4,000,000, but not uncommonly 5,000,000 or even higher. Ward[11], among others, has stated that in the early stages of the disease there may well be an actual increase of red cells with proportionally less increase of hemoglobin, but on account of an increase in blood volume, an illusion of anemia occurs. If, however, it is found that the volume is decreased, with the undersized cells which occur, a similar count of red cells will be obtained. As the blood formation works under strain, actual reduction in hemoglobin occurs, which becomes marked, and with this there is slight reduction in the red cells; if increases of volume without increases of erythrocytes occur we must recall that the absolute numbers of red cells in the body may not diminish.

The red cells themselves, besides being markedly achromic, show further evidence of defective formation by usually being undersized. Variations in their size occur but never to a marked degree, while microcytes practically do not occur. The shape of the erythrocytes is usually essentially normal; variations may occur but are never marked. Absence of any rapid regeneration is seen in the rarity of polychromatophilia and lack of increase of the reticulated cells. Nucleated red cell crises were first described by von Noorden[5] in a case of chlorosis, but it has since been shown that crises of nucleated red cells are rare in this disease, though in the severer cases a few nucleated red cells occasionally occur. With improvement, increases of the number of red cells, often to normal or above, occur long before the cells regain their size or proper complement of hemoglobin.

That part of the marrow which is concerned in the production of white cells seems to be little affected in the early stages as the leukocytes are normal or slightly increased. Distinct increases are usually transitory, even when occurring complications may be the cause and need to be ruled out before attributing the change to the chlorosis. Later a leukopenia occurs with rarely a lymphocytosis, indicating inactivity of the marrow.

Reports on the platelets in chlorosis are sparse. It appears that the platelets not infrequently are increased, and often very markedly so. Hence the megakaryocytes of the marrow are able usually to increase their activity.

The diagnosis of chlorosis should not be difficult because distinct anemia in young women without obvious cause is seldom of any other type. This fact taken together with a blood picture of the type described should establish the diagnosis. Some of the cases of what appear to be mild grades of simple chronic anemia, occurring in young women without definite causes, may well be simply cases of poorly defined chlorosis. Thus it seems that intermediate cases between these two conditions occur, so that it is difficult to say, for example, if a case is definitely one of chlorosis with gastro-intestinal symptoms, or whether a gastrointestinal putrefaction is the cause of an anemia. Besides other forms of anemia, tuberculosis, neurasthenia, hyperthyroidism, nephritis and early pregnancy are the conditions that particularly may be confused with chlorosis. Careful examination of the patient, including examination of the blood and urine, will readily rule out these conditions.

It is not to be lost sight of that, though the blood picture of typical chlorosis is rather characteristic, it may occur in other conditions, and that the less marked pictures are essentially like those occurring in simple chronic anemia. The red cell histological picture may be like that of anemia due to blood loss except for the fact that a considerable increase of young red cells will rarely be seen in chlorosis.

(3) MYELOPHTHISIC ANEMIA

By myelophthisic anemia is meant an anemia dependent upon a crowding out of the normal marrow tissue by tumor or tumor-like formations. The result is that the activity of the remaining tissues becomes increased, and this increase may be of a very marked degree. This activity is apparently not always proportional to the amount of infiltration, which suggests that some additional "irritative process" plays a part in some cases. Such a process, crowding out the erythrogenic centers, occurs as an integral part of the disease, myelogenous leukemia. In lymphatic leukemia of the various types the increase of the abnormal cells in the marrow displaces not only the red and white cell elements but also the megakaryocytes, so that diminution of platelets is a feature of this condition, as is diminution of the marrow white cells. Sometimes the process is so severe that the normal marrow is wholly transformed and essentially no normal tissue is found at autopsy, so that the red cells and other marrow elements in the peripheral blood will have all the features of an aplastic anemia.

The rare condition of osteosclerosis will also act to crowd out the marrow. Similarly tumors, not only of the bones and marrow itself, as myeloma and chloroma, but metastatic tumors resulting particularly from hypernephroma and cancer will obliterate a considerable part of the marrow cavities. In such conditions reversion to the embryonic sources of blood formation may occur, so that the liver and spleen may show active hematopoiesis. With metastatic tumors we not uncommonly see great numbers of blasts and other forms of early marrow cells in the circulation, and in such processes tumor cells may occur in the peripheral blood.

In an individual, where a primary tumor is suspected, the finding of many blasts and other early marrow cells should suggest that marrow metastases had occurred. As Jack and Teacher[21] recently, and others previously, have pointed out, such findings do not always occur with extensive metastases. We believe this is because in some instances, as in Jack and Teacher's case, the marrow has been so inactive due to the early disease that the cells are not there to come out. Hence what cells appear in the peripheral blood would seem to depend upon what cells there are in the marrow to come out. In some instances, metastases may lead to an anemia where the platelets are so decreased that a purpura hemorrhagica ensues, this being previously dependent upon a crowding out of the giant cells of the marrow. Such a phenomenon may be apparent when the patient is relatively little anemic, as we have recently seen in an unusual case of an exceedingly rapidly growing metastatic hypernephroma. The red cells in this case at the time the platelets were scant showed many signs of regeneration and the polynuclear leucocytes were increased. It would seem, in light of the autopsy, which showed multiple small metastases throughout the marrow of various bones, that the chief reason that the red cells dropped more slowly than the platelets was the fact that the former live longer in the circulation than the latter. An additional reason may be that there is probably proportionally more red-cell-forming tissue than platelet-forming tissue in the marrow.

(4) APLASTIC ANEMIA

When referring to simple chronic anemia, particularly that dependent upon defective blood formation, we referred to the fact that in probably many instances grouped under this general heading, some degree of blood destruction occurred, but that in other instances there was none, defective formation being the sole cause of the anemia. It was noted that in some such instances patchy atrophy of the marrow might occur. Such a condition represents a partial aplasia that may be recovered from. This, however, may progress to a state of complete aplasia; that is, where the marrow consists of practically nothing but yellowish fat. The best example of such a progress of events is seen in benzol poisoning, and somewhat similar changes have been reported by Krumbhaar[22] in certain forms of gas poisoning.

Besides known conditions that may cause aplasia, including anemias of different types that may terminate with aplasia, there is a condition with aplasia of the marrow that at present has a distinct enough clinical picture to be considered a disease entity. This is known as idiopathic aplastic anemia. The blood picture with any aplastic process will be essentially the same, whether it is produced by idiopathic aplastic anemia or by aplasia resulting from known causes or in the course of some other anemia.

Numerous conditions may cause aplasia of the marrow, and among them are the following: In certain instances of the various forms of hemolytic anemia, aplasia may occur, perhaps because the overwhelming destruction in some manner poisons the marrow, or because the cause of the anemia itself acts directly on the marrow. The aplasia resulting from trinitrotoluol poisoning and that occurring in acute hemolytic anemia due to sepsis are examples of this. In other instances with little or no hemolysis, aplasia may occur as in overwhelming sepsis, rarely in pneumonia, typhoid or diphtheria. In these cases the marrow is poisoned directly, just as with benzol. Other instances, where aplasia without significant hemolysis occurs, are when excessive amounts of radium or Roentgen rays are given. Untreated myelogenous leukemia may terminate with an aplastic fatty marrow. True pernicious anemia, as well as the anemia due to the fish tapeworm, may rarely terminate with aplastic marrow. Some have considered that idiopathic aplastic anemia is a form of pernicious anemia, but it seems that it is a distinctly different condition and is to be sharply distinguished from it.

Secondary Aplastic Anemia

Aplasia resulting from known causes or secondarily in some recognized form of anemia or disease process, may best be called secondary aplasia in contrast to the disease idiopathic aplastic anemia. Precisely why aplasia occurs we do not know in many instances, but it would seem to be dependent upon a specific poison for the marrow, as benzol is. In other instances, as in sepsis, we may assume that the toxins which normally act in another way have become perverted so that they spend themselves on the marrow. In some instances such an action may perhaps be coupled with some congenital weakness of the marrow. There is no evidence to suggest that such a process may be produced by simple exhaustion of the marrow by repeated hemorrhage alone. This has been well shown by Boycott and Douglas[23].

Idiopathic Aplastic Anemia

From analogy to cases where poisons and toxins produce aplasia, as well as from the clinical and pathological nature of idiopathic aplastic anemia, it seems reasonable to suppose that idiopathic aplastic anemia is dependent upon some form of poison acting directly on the marrow itself. The difference between secondary aplasia and idiopathic aplasia may be summed up by saying that in the former we recognize a source for toxin formation, while in the latter we do not.

The term idiopathic aplastic anemia is thus reserved for a disease, first described by Ehrlich[24] in 1888, the etiology of which, as stated, is unknown. The disease runs a progressively downward, fatal course of but a few weeks' duration, seldom as long as six months, and usually less than two and a half months. It particularly occurs in individuals between fifteen and thirty years of age, females being perhaps more susceptible than males.

The recent papers by Musser, Jr.[25], J. P. Schneider[26], L. W. Smith[27] and Minot[28, 29], and that of Cabot[30] in 1908, summarize what is known about this condition and discuss the various views about it.

The onset is marked by no particular symptoms except those referable to anemia per se, and such symptoms increase, of course, as the anemia progresses. The individuals at times give a history of not having felt strong or perfectly well for some weeks or months before the definite symptoms occur from which the onset of the disease is usually dated. In some instances a history of some infection is obtained as occurring just prior to such a period of somewhat poor health. At times one will learn that the individual has never been very strong. This latter type of history is perhaps not rare in various essential blood disorders, and might suggest that a congenital weakness of the hematopoietic functions played at times a part in the production of such diseases. In this connection, it is interesting to note that an enlarged thymus, which occurs in this asthenic type of individual, has been reported in some instances of idiopathic aplastic anemia.

The patient, of course, appears pale. Usually there is a white pallor, though at times it is a trifle waxy. The sclerae are of a dead white color and never yellowish.

Symptomatic purpura hemorrhagica of at least a slight degree occurs in all cases with its usual features, including petechial hemorrhages; at times severe hemorrhages from the mucosae occur, dependent in some manner on the diminished platelet content of the blood. Hemorrhages of such a nature may occur early, but usually they are late. There are no particular signs, referable to the internal organs, that occur in idiopathic aplastic anemia, though it is to be noted that considerable fever is common, sometimes, but by no means always, associated with recognized sepsis. Sepsis, especially oral sepsis and often associated with hemorrhage, may develop in aplastic anemia. Thus we must distinguish cases of anemia resulting from sepsis from those where sepsis has appeared in the course of an anemia.

Pathologically in some cases, as in Smith's[27], large amounts of hemosiderin have been found in the liver and other tissues, but this is more usually not the case. This finding has caused some to consider that blood destruction was an important factor in idiopathic aplastic anemia, but other evidence, as diminished amounts of blood-derived pigments in the excreta and plasma, absence of microcytes and enlargement of the spleen, indicates that this is not the case, and the presence of hemosiderin can be explained by hemorrhages and in other ways. However, it is not to be lost sight of that we may have aplasia occurring in hemolytic anemias, in which instances hemosiderin deposits may be found. Likewise it is quite possible that there may be a group of acute idiopathic hemolytic anemias which terminate with aplasia. That such may be the case is evidenced by the report of a group of cases in children considered to be of such a nature by Kleinschmidt[31]. Besides the occasional finding of hemosiderin deposits no important pathological findings occur in idiopathic aplastic anemia except the typically perfectly aplastic marrow which consists of essentially nothing but yellowish white fat in the marrow cavities. Of course, the "toxin" progressively acts on the marrow, so that at a given time before the process is complete, there will remain areas of the marrow not as yet destroyed, for no toxin can at once render an entire organ degenerative. Hence, at post-mortem, small foci of hyperplastic marrow may be found. Such areas may try to regenerate the blood. This type of process may go on to a considerable degree before the trap is sprung so far that regeneration cannot ensue, as experimentally can be seen in benzol poisoned animals as studied by Selling[32] and Hurwitz and Drinker[33]. In some of the instances of secondary aplasia it would seem as if the effort at regeneration was more marked than in the idiopathic cases.

The blood picture of aplastic anemia shows what is to be expected from the pathology of the condition, namely, no or very little evidence of regeneration of the three formed elements originating in the marrow, as shown by the following findings:

(*a*) The red cells usually drop to a million or below before death. They appear quite well filled with hemoglobin and the color index is but slightly reduced. There is little or no variation in shape, and relatively little variation in size, particularly when one considers the degree of anemia. Polychromatophilia, stippling and nucleated cells are usually absent or rare. The reticulated cells are commonly diminished or even absent, though at times transient increases above their normal percentage may occur, dependent upon the remaining tissue putting forth what young cells it can.

(*b*) The white cells always show a leukopenia, more marked as the disease progresses. This leukopenia consists in an absolute diminution of the polynuclear cells and nearly always there occurs a disappearance of the eosinophils. Thus a relative but not absolute lymphocytosis occurs, the lymphocytes being, at the time the anemia is well marked, about 70 per cent. of the white cells. They are of the small type. Atypical and abortive polynuclears are apt to be seen, and granular mononuclear cells are rather often increased, particularly when the process is not far advanced; but distinctly early bone marrow white cells, like myeloblasts, are exceedingly rare.

(*c*) The platelets which are often neglected in studying the blood and which are most important elements[34], are markedly decreased, often nearly absent. They are usually slightly larger than normal.

The earlier in the course of the disease that the blood is examined, the less marked will be the diminution of platelets and bone marrow white cells, and the more usual the presence of a few young red cells. Further evidence of aplasia is seen in the absence of any response on the part of the marrow to transfusion.

The fragility of the red cells to salt solutions is abnormal and of the following type: The cells begin to break up in about the same strength salt solution as they normally do, not infrequently in a weaker strength, but complete hemolysis occurs in a higher percentage of salt solution than normal. This type of fragility is to be looked upon as an undesirable one. It may sometimes occur in other conditions, as simple severe depression of hyperplastic marrow, and, in some cases, of idiopathic purpura hemorrhagica.

If one keeps in mind the blood picture of aplasia, including the manner in which the red cells act to various strengths of salt solution, the clinical picture of the idiopathic disease frequently will be recognized clinically, though the absolute diagnosis cannot be established except at autopsy.

It is to be recalled that an essentially similar blood picture may result from replacement of the marrow by abnormal cells, but in such instances it is usual to see more evidence of activity of the remaining red cell tissue than in aplastic anemia, some of which may be dependent upon hematopoiesis in the liver and spleen. Such a process of formation appears not to occur in idiopathic aplastic anemia. The clinical findings in cases of myelophthisis will particularly serve to distinguish these cases from aplastic anemia, as well as the fact that other blood findings as those in leukemia will often occur in addition to those of aplastic anemia.

There are instances where the marrow at autopsy shows hyperplasia when the blood findings have been much like those of aplasia and perhaps identical to it. Such a state of affairs is probably dependent upon some process that inhibits or depresses blood cell formation but does not destroy the marrow, and may occur following repeated hemorrhages in Banti's disease and typhoid fever among other conditions. Drinker has called attention to the fact that red cells must proliferate steadily in order to reach the circulation. In accordance with this view temporary periods of arrest of growth may imitate the blood picture of aplasia. This sort of a condition is also usually distinguished from at least idiopathic aplastic anemia by differences in the clinical picture presented, and is more apt to occur with relatively higher red counts than in advanced aplastic anemia, and may let up so that recovery occurs.

It is rather a feature of aplasia to find fairly normal looking red cells in the presence of very low red counts. This, taken together with the other evidence of marked marrow insufficiency, more often indicates aplasia than any other condition. Should we find, with a very low red count, a similar picture but with a high color index and an occasional unduly large and oval-shaped red cell, one should suspect that he was dealing with an instance of aplasia that has developed in a case of pernicious anemia. In pernicious anemia with such a picture the marrow may not be fatty, but red, though distinctly abnormal, so that the picture may depend upon a marrow so deranged and depressed that it simply is unable to act.

The chief condition that is likely to be confused with idiopathic aplastic anemia is idiopathic purpura hemorrhagica. This is because both conditions present in common, anemia and purpura, and may run a similar course, and because symptomatic purpura hemorrhagica occurs in aplastic anemia. Purpura hemorrhagica is to be considered as a condition in which we have bleeding from one or more mucous membranes, often with purpuric skin lesions associated with diminution of blood platelets, a delayed bleeding time, and a nonretractile clot, the coagulation time being normal or slightly delayed, rarely much delayed. Purpura hemorrhagica is perhaps more usually secondary to some recognized cause or disease, as tuberculosis, pernicious anemia, aplastic anemia, etc. When purpura hemorrhagica accompanies some other disease, it is considered a symptom. When it is not secondary to a recognized disease, it constitutes what is often regarded as a disease entity called idiopathic purpura hemorrhagica. As such, it may be acute, subacute or chronic, of a continuous or intermittent nature, and congenital and hereditary types exist which are commonly confused with hemophilia. It is with the acute and subacute type that idiopathic aplastic anemia is confused. They both occur in people of similar age, but idiopathic purpura hemorrhagica is rather more common in children than is aplastic anemia.

It is important to distinguish the conditions because individuals with aplastic anemia do not recover, and those with purpura hemorrhagica may recover, though fatality is common, particularly in the acute and subacute form. Likewise, distinction is desirable between these conditions because transfusion in purpura hemorrhagica may be very valuable and in aplastic anemia yields no significant results. In idiopathic purpura hemorrhagica hemorrhages occur early before the anemia is marked in contrast to aplastic anemia, when they usually occur after the anemia is well established, for the platelets are reduced early and usually rapidly in purpura hemorrhagica, and in aplastic anemia progressively and more slowly. Also purpuric rashes and hemorrhages are often more marked in purpura hemorrhagica than in aplastic anemia even though the platelet count may be the same. The blood picture of the two conditions is similar in that marked diminution of the platelets occurs in both; but in typical idiopathic purpura hemorrhagica there will be found evidences of regeneration of the white cell and red cell elements of the marrow, as evidenced by increased numbers of bone marrow white cells and young red cells in the circulation, these being particularly marked following the hemorrhages which contribute to the anemia. Such a picture is in contrast to that of aplastic anemia with its leukopenia and but few young red cells even following hemorrhages.

The marrow in acute purpura hemorrhagica is often hyperplastic, and even increases of the giant cells may occur, so that in this condition we may suppose that an unknown poison has caused either some form of decreased activity of the megakaryocytes or that there has been a destruction of the platelets in the circulation. There appears to be a group of cases intermediate between idiopathic aplastic anemia with symptomatic purpura hemorrhagica and idiopathic purpura hemorrhagica. From such cases it is suggested that these two conditions may perhaps be not distantly related; for one can find cases of these idiopathic conditions where the blood picture can be interpreted as showing all degrees of involvement of the three chief elements of the marrow. It would seem that in many such instances, the marrow is deeply implicated in the disease process. In pure aplastic anemia the disease process is directed towards all the marrow elements, while in idiopathic purpura hemorrhagica it is directed intensely towards the platelets. In the intermediate cases, it would seem that the process acts less specifically, involving in varying degrees the other bone marrow elements in addition to platelets. If the process of rapid destruction of the platelets occurs, either the result of it or the immediate cause of their destruction may perhaps later, to a greater or lesser degree, cause a depression or aplasia of the marrow as a whole. Such a state of affairs would be similar to that which may be seen when aplasia develops in certain hemolytic anemias. The cases of congenital purpura hemorrhagica may perhaps be somewhat comparable to congenital hemolytic jaundice, in that in the former the platelets may suffer destruction but without evidence of regeneration, while in the latter the red cells are destroyed, though with evidence of regeneration. The other alternative to explain the diminution of platelets in the congenital cases is, of course, a congenital deficiency of the platelet forming elements.

We have previously alluded to the fact that a myelophthisic condition may be confused with aplastic anemia, and it, also, of course may be confused with purpura hemorrhagica. This is particularly true in instances of the nonleukemic phase of a lymphatic leukemia of the acute type, when symptomatic purpura hemorrhagica ensues dependent upon a crowding out of the megakaryocytes of the marrow. In such cases the presence of enlarged lymph tissue is the rule and does not occur in aplastic anemia or purpura hemorrhagica; but appreciable enlargement of such tissue at times may not be evident in such a leukemia. The demonstration of a qualitative variation from normal of the lymphocytes, so that increased numbers of abnormal lymphocytes occur, is of great importance in the diagnosis, for practically all the lymphocytes present in aplastic anemia are normal small lymphocytes. The percentage of lymphocytes may not be high in the nonleukemic phase of leukemia but as a rule it is much higher (95 per cent.) than it is in aplastic anemia.

ANEMIA IN WHICH BLOOD DESTRUCTION IS USUALLY MARKED AND WHERE THE ANEMIA IS PARTIALLY OR WHOLLY DEPENDENT ON ABNORMAL BLOOD DESTRUCTION

(1) PERNICIOUS ANEMIA

Pernicious anemia (Addison-Biermer anemia) is an idiopathic disease that progresses slowly, usually by remissions, to a fatal outcome.

(a) *Etiology and Age Incidence*

The cause of this disease is as much of a mystery today as it was when described by Addison in 1849[35], and in 1855[36], and by Biermer in 1872[37].

It is generally conceded that it is a chronic hemolytic anemia and that the myeloid tissue is also deeply implicated in the disease process. Vogel[38], Moffitt[39, 40], Squier[41], and others, have recently discussed the disease. Some, as Cederburg[42], consider that it is the result of a gastrointestinal disturbance which allows undigested proteins to be absorbed and in their further course to act as protein poisons, or which allows the absorption of hemolytic toxins produced in the process of intestinal putrefaction. Dietary deficiency, as in pellagra, might be associated with such a process. Others, as Hunter[43], consider chronic sepsis to be an etiological feature, while some consider that it is an infective disease of unknown etiology. Eppinger[44], among others, considers the disease to be the result of altered lipoid metabolism or to a condition of hypersplenism. Abnormal splenic function is undoubtedly present, but this would seem to be but a link in the chain that makes up the unknown cause. The hemolytic agency has been sought for by many workers. Eppinger[44] and King[45] are inclined to attribute this to the unsaturated fatty acids. This is not quite in accord with McPhedran's work[46]. Yet we do know from the work of Faust[47] and Adler[48] that such substances can produce hemolysis and anemia in animals, and that hemolytic substances are associated with the cause of the anemia[49] due to the fish tapeworm, and the anemia of the horse[50, 51], due to the larva of a fly in the intestines. Also, it has been shown, particularly by Bloor and McPherson[52], that a high fat content, along with a low cholesterol content (an antihemolytic substance) and leichitin content, occurs in the blood plasma in pernicious anemia. Iwao[53] considers amino acids to be the hemolytic agency. It is also worthy of note that certain chemical substances, such as saponin[54, 55] and phenylhydrazin, may produce a hemolytic anemia in animals with a blood picture that resembles pernicious anemia in humans, but beyond this no real resemblance occurs.

Much might be written concerning the etiological theories of pernicious anemia and the many experiments conducted to throw light upon this, but suffice it to say that we do not know the cause. It is probable that the manifestations of the disease depend on a variety of partial causes which are differently associated in different cases, the primary one being unknown. This might well be a constitutional abnormality, an inherent weakness, which permitted a reversion of the hematopoietic functions to a somewhat embryonic type, not unlike what may occur in cancer, as referred to by McCaskey[56]. And it is true that pernicious anemia may occur in the same family, though this is unusual. Bartlett[57], and Patek[58] among others have reported such cases. At times a rather striking family history, particularly in brothers and sisters, is obtained in undoubted cases of pernicious anemia that are not instances of hemolytic jaundice. A striking instance of this, which we have recently observed, is as follows: A brother and two sisters died of pernicious anemia between the ages of sixty-one and sixty-three. A male cousin on their mother's side also died of pernicious anemia at the age of fifty-nine. By history it was learned that a maternal uncle and aunt died of this same condition.

The disease is particularly one of adult life and though commonest between the ages of forty and fifty-five, it is frequently seen in older individuals. It is distinctly rare under the age of thirty, and very few authenticated cases are reported under the age of ten. D'Espine[22] has collected these. Pernicious anemia appears to be commoner in men than in women. In general it is the older patients that belong to what is referred to below as the myelotoxic type and it is the younger that belong to the more hemolytic type.

(*b*) *The General Course of the Disease*

The diagnosis of pernicious anemia, for reasons given below, is frequently not made until the disease has progressed to a considerable degree. The diagnosis is to be made quite as much from the symptomatology as from the blood findings. There are certain symptoms and laboratory findings that are quite characteristic of the condition. Before taking these up in detail, a consideration of the general course of the disease will be discussed, for this is most important to comprehend in order to make a correct diagnosis.

Though one does not know the cause of the disease process, we do know that there occur an abnormal red cell destruction and an abnormal type of blood formation. It is thus evident that at a given time the number of blood elements merely represents the balance between blood destruction and blood formation. It is the nature of the disease to permit considerable fluctuation in this balance, so that one of the features of the disease is its progress by relapses and remissions. The cases can be roughly divided into groups dependent upon this character, as Archibald[23] and Minot and Lee[24] have recently suggested.

1. Cases of a rather acute nature that progress steadily downward to a fatal termination, the blood destruction always being in excess of formation, and never letting up. Such cases are not to be confused with acute hemolytic anemia dependent upon sepsis, or with idiopathic aplastic anemia.

2. Cases characterized by marked or fair remissions in the course of the disease, occurring quite sharply or gradually. There is usually considerable hemolysis during relapses and little during remissions; hemolysis may be absent during remissions.

3. Cases that show persistently a considerable degree of hemolysis with relatively slow, never very striking remissions, but which do not have serious relapses, except after years or terminally. These cases appear to approach the condition of acquired hemolytic jaundice.

4. Cases of a chronic nature that slowly progress downward though interrupted by mild remissions and rarely by moderate remissions. This type merges directly into the next.

5. Cases of a continuous chronic nature that very slowly progress downward with usually no or only very slight remissions and with a sluggish. inactive marrow.

The cases of these last two groups have relatively less increased red cell destruction than the first groups, and may be termed myelotoxic in contrast to the others that are more hemolytic and have a more active marrow reaction.

Statistics on the duration of the disease are notoriously unreliable on account of the difficulty of telling when the disease actually began, as will be alluded to below. However, the average duration of cases, after clear cut symptoms have developed, is about two to three years. It is not uncommon for cases to die in less than a year, but rarely under five months. On the contrary it is not so very rare to have cases live for seven years, while rarely they may live for a much longer period, over ten years. There are records of cases living twenty years after a first relapse.

Following a definite relapse one remission of some grade is the rule; the usual length of the first remission is about ten months. However, five relapses and remissions are not uncommon and many more may occur. Some may be of but a month's duration, while in other instances they may be over ten years apart. As a rule, each succeeding remission is less marked in degree and of briefer duration than the preceeding, though this is not always the case. It is also to be noted that an individual usually will remain in a relapse some weeks, not uncommonly as long as nine months, and sometimes as long as two years and perhaps longer. A long relapse may be followed by an excellent remission, though as a rule the longer the relapse persists after some weeks have passed, the less is the likelihood of any satisfactory remission.

(c) *Symptoms and Signs of Pernicious Anemia*

The onset of the disease is gradual, which accounts for the infrequency with which the early stages come under the notice of physicians and why early diagnosis is seldom made. General weakness or abnormal fatigue are the commonest symptoms of which the patient is apt to complain. It is not unusual to find when the case is first seen, that though such symptoms have been particularly present in recent weeks or months, for a much longer period, a matter of years sometimes, the patient has not been "as strong as formerly" or has had "indigestion" for a long time. This is truer of the older rather than of the younger cases.

There are certain symptoms that are more or less peculiar to pernicious anemia. These are symptoms referable to the gastrointestinal tract, especially a periodic sore tongue and mouth, and to the central nervous system, especially a persistent paresthesia of the hands and feet and symptoms of combined sclerosis. Such symptoms are frequently not significant enough for the patient to mention, which is an important point, because, when specifically asked for and looked for, they will be much more commonly found than when the patient volunteers the information. These symptoms, as Schaumann[62] and many others have noted, may be the first the patient complains of and serve as important positive evidence on which to base the diagnosis. By direct inquiry for such symptoms from a patient who feels below par, they may be obtained and become the most important clue to the diagnosis, and, combined with a study of the blood, will make the diagnosis.

The Gastrointestinal Symptoms and Signs

The Tongue and Mouth.—The condition of the tongue and mouth is most important, as has been noted by Hunter[43] and emphasized by others [63, 64, 65, 66]. In fully 45 per cent. of the cases, and probably more, the patient will have subjective, disagreeable sensations referable to this region sometime during the course of the disease, more commonly relatively early than late. These disagreeable sensations consist of a burning of particularly the anterior half of the tongue. A soreness or rawness is present, often described as if one had taken acid. Frequently it is painful for the individuals to take any kind of food, but particularly hot, acid, or spiced food. Tenderness is not uncommonly noted when chewing. It is extremely characteristic for such symptoms to occur periodically, and it is unusual for them to remain at their height for over three weeks, while the severity is commonly for but a few days. The tongue appears raw and red and often is indented by the teeth; red inflamed patches of superficial ulceration or small shallow ulcers may be present, and not infrequently small inflamed vesicles occur, which in some instances may become quite large and hemorrhagic and leave evidence of old hemorrhagic effusions beneath the surface of the tongue. These features are usually more marked about the tip and edges of the tongue. As the process progresses with recurring soreness, atrophy occurs so that the tongue appears smooth, shiny and flabby, and the papillae are wasted. A tongue with such an appearance not uncommonly occurs in pernicious anemia without recurring soreness. This glossitis is considered by some to be pathognomonic of the disease. Whether it is or not, it is certainly most unusual to see an exactly similar recurring process in any other condition than pernicious anemia. It would seem as if this glossitis were not infective in nature,, though sepsis as pus from about the teeth, commonly seen in these cases, may distinctly aggravate it.

A similar process may occur on any part of the mucosae of the mouth, particularly the buccal mucosa and inner lower lip, where denudation of epithelium may be quite marked and very painful. Apparently this process may extend down the esophagus, for sometimes the patient complains of burning and rawness well back in the throat and under the sternum, associated with active mouth lesions. Another feature that has recently come to my attention is that an actual partial loss of taste may occur with the atrophy of the tongue, probably due to atrophy of the taste papillae. This is not to be confused with a disagreeable taste that the individuals complain of, dependent either upon the condition of the mouth or gastrointestinal tract.

To emphasize again the fact that symptoms referable to the mouth may be the clue to the diagnosis, the following experience is cited. Recently we have seen three individuals who sought relief for a sore tongue and claimed that they were otherwise well. On account of this, they were referred to a laryngological department, where local treatment was given and the soreness subsided after about two weeks. At this time they were told that the soreness was of no particular consequence. Some months later we found these individuals to have undoubted pernicious anemia as evidenced by their history, their blood findings, and a recurrence of their tongue symptoms, though even then they were but slightly anemic.

Stomach and Intestines.—Symptoms referable to the stomach and intestines are also common in pernicious anemia, and frequently these are the first symptoms spoken of by the patient. Practically every case has symptoms referable to these organs at some time in the course of the disease. These symptoms would appear to be dependent in some instances upon actual atrophy of the mucosa, in others, they may be dependent upon improper secretion of the gastrointestinal juices; while at times the physiological cause is unknown. It is, however, a fact, as Martius and Lubarsch[67] among others have shown, that absence or at least very marked diminution of the hydrochloric acid (achlorhydria) of the stomach is found in practically every case. A very recent paper by Friedenwald and Morrison[68] reviews the subject of the gastrointestinal disturbances in pernicious anemia and the authors find the gastric secretion normal in but 7 per cent. of their cases. Achylia, or achlorhydria, is a feature of the disease and remains present whether gastrointestinal symptoms are severe, mild or absent, or whether the individual is in a state of remission or relapse. Achylia may be the first indication of the disease and be present for some years before definite anemia or any clear cut blood changes are observed.

The symptoms referable to the stomach and intestines are loss of appetite, nausea, vomiting and diarrhea, paroxysms of which are more or less prominent. At times there is diarrhea alternating with constipation, while in some instances constipation alone is prominent. Indefinite abdominal pain, with a sense of fullness, pressure and distention, usually associated with the passage of an excessive amount of gas and often putrefactive stools, commonly occur. There occur, also, frequent paroxysms of abdominal pain, with or without diarrhea, some of which may be dependent upon spinal cord changes and resemble the gastric crises of tabes dorsalis. It is not at all uncommon to see periodicity of the gastrointestinal symptoms similar to the periodicity of the tongue symptoms, so that periods of good digestion will alternate with periods of bad. The periods of bad digestion do not necessarily coincide with a falling red count, a decreased hemoglobin percentage or increase of red cell destruction, though they are more apt to occur when the former is lower and the latter greater. It does seem, however, that such symptoms are frequently related to the blood volume [69, 70]; they appear to be severer when the volume is less, and with their increase, particularly with diarrhea, the volume diminishes still more, and until the volume is increased either by nature in some manner or by artificial means, the symptoms persist.

Symptoms referable to the stomach and intestines may be present for a long time, even ten or more years, before the individual becomes outspokenly sick or anemic, or has his first definite relapse. This is not uncommon. Such cases as these are commonly diagnosed as some type of chronic gastrointestinal disorder. They have been operated upon for chronic appendicitis, chronic duodenal ulcer, etc. and the surgeon has been disappointed at finding no definite lesion. In such instances the blood picture is not clear cut and demands careful critical study; usually with care the diagnosis can be made, while at other times in such cases it is perhaps impossible to do so.

Weight.—Because loss of weight is commonly dependent on an improper amount of food or faulty absorption of food, it will be referred to here. Preservation of the fat layer and relatively little loss of weight is a feature of the disease. This occurs in about 60 per cent. of the cases. Many patients, however, do lose weight[71, 13], and in 40 per cent. a considerable loss of weight occurs. It is usual to have in this group of patients rather marked gastrointestinal symptoms, though exceptions occur. Loss of weight not infrequently occurs with relapses, to be regained in remissions. A most striking instance of this was seen in a man weighing 180 pounds who had twelve rather rapid relapses and remissions. In the first five relapses he lost each time between 35 and 50 pounds, and gained back to about 180 pounds with each remission. Less marked instances are commonly seen. Loss of weight is thus to be looked upon as an undesirable feature, but variations in weight are not by any means always parallel to the red count and increases of fluid in the tissues may of course, at times, be the cause of undesirable gains in weight[72]. It is definitely to be noted that loss of weight may and often does occur in this disease; this is important because commonly it is incorrectly said that loss of weight serves as a crucial point in distinguishing pernicious anemia from cancer.

The Central Nervous System, Symptoms and Signs

Like the gastrointestinal symptoms and signs, those referable to the central nervous system are more or less peculiar to pernicious anemia and are a feature of the disease. The articles by Putnam and Taylor[73] as well as those by many others[74, 75] describe these symptoms well. They are referable to patchy degeneration of the cord and brain, a subacute combined sclerosis commonly occurring. Toxins of some nature and not the anemia per se are responsible for these changes, and similar changes can occur in other diseases. Quite probably the cord lesions and the anemia have a similar common cause. Recently Blankenhorn[76] has observed that cases with the largest amount of bile salts in the blood have the greater involvement of the central nervous system, and suggests that they are responsible for the neurologic manifestations. This might suggest that those cases with the greatest hemolytic activity have the greatest central nervous system involvement. However, this does not seem to be the case as measured by our present methods of determining increased red cell destruction, for the bile salt content of the plasma does not run parallel with the blood derived pigments in the plasma. It is important to note that cord and sometimes mental symptoms may appear long before there is clear cut evidence of underlying pernicious anemia, so that such symptoms may be the first indication of the disease. It is not at all uncommon, if one is on the lookout for cord symptoms, to find them early in the disease, particularly in older individuals. They are nearly always present when the disease occurs in individuals over 55 years of age, being less common in the younger. Woltmann[77] recently found in 150 cases indisputable evidence of destruction of the nerve parenchyma in 80.6 per cent., while 12.7 per cent. of the cases sought a physician purely on account of the nervous symptoms. These symptoms may dominate the picture and the blood never go to a very low level; the individual will die of the cord changes rather than of the anemia. The lack of severe anemia does not by any means necessarily indicate that death is not far off, and many cases have marked cord involvement with the hemoglobin over 75 per cent. and the red count about 3,000,000.

It is much more common to have relatively trifling central nervous system symptoms, such as slight disorders of sensation, as numbness and tingling of the hands and feet, than those of a marked combined sclerosis. Cases of other forms of anemia may exhibit such symptoms, but it is distinctly rare to find these symptoms marked and persistent in other anemias than pernicious anemia, and then only when the anemia is severe, while pernicious anemia cases commonly exhibit such symptoms when the anemia is slight. Cases with only paresthesia may show no definite spinal cord changes at autopsy.

There may occur, also, slight motor disorders, some of which may be due to weakness from the anemia, but the majority are due to changes in the cord. The more marked nervous symptoms may simulate other ataxic or spastic conditions. This is natural, as the pathology is similar, namely, in some cases, degeneration of the lateral columns, in others, of the posterior columns, and usually some degeneration of both together. When the former are particularly involved, we have spastic gait, increased reflexes and some degree of paralysis; and when the latter are involved, tabetic-like symptoms and signs, namely ataxia, lightning pains, girdle pain, and abdominal crises, and absent or diminished reflexes with involvement of the sphincters of the bladder and rectum.

Sometimes the cord symptoms presented during life seem relatively mild compared with the rather gross lesions found post-mortem, while in others, the reverse is true. In view of the fact that the foci of sclerosis may be found in various parts of the cord, the symptoms will vary accordingly, and not uncommonly we get an incomplete clinical picture of spinal disease rather than a clear cut picture of spastic, ataxic, or combined system disease. Rarely hemorrhages into the central nervous system may give an unusual picture. Some of the symptoms may be dependent upon a degeneration of the peripheral nerves themselves, a true multiple neuritis occurring. A diffuse myelitis is rare, and sensory symptoms, except simple paresthesias and anesthesias, are unusual. Pain, which may be intense upon motion of the extremities, is rather rarely seen. Disturbance of the sensations of heat and cold are usual, while disturbance of bone sensation, as tested by the vibrations of a tuning fork, is relatively common.

Though symptoms referable to the spinal cord will be found to occur in practically all cases over the age of fifty-five if they are looked for, it is unusual that a marked combined sclerosis develops before any very definite anemia, but such may be the case and precede it even by some years. Critical blood examinations, however, will in many such instances tell the character of the disease. It is much more common to have definite anemia precede the combined sclerosis by some time, usually about ten months, though occasionally both may start at the same time. Sometimes the spinal cord symptoms develop with great rapidity; more usually rather slowly.

The degree of degeneration in the spinal cord is not a measure of whether remissions will occur or not. When definite evidence of degeneration of the spinal cord is once present, it will always remain, even though the patient may have a marked remission. The symptoms referable to the cord changes may become slightly better with remissions, but no marked improvement will occur. When simply paresthesias are present, they are not infrequently lessened and may become absent with improvement in the blood; while when pain upon motion occurs, it is apt to lessen as time goes on, whether the blood improves or not.

In some cases mental disturbances may develop, and like the cord symptoms these may precede the onset of the anemia, but it is much more usual for them to follow it and be a sign that no remission will occur. The recent papers by Barrett[78] and Woltmann[79] are particularly illuminating on this phase of the subject. Degenerated areas of the type first described by Lichtheim[80], such as are typically found in the posterior and lateral columns of the cord, are found in the brain when properly looked for. Practically any form of psychic alteration may occur from the mildest types to the most intense. In many instances an underlying hereditary predisposition will be found, and some of the well marked psychoses associated with pernicious anemia are probably not dependent upon the degenerated areas but are brought to the surface by the disease. While, as Woltmann says, the manifestations of somnolence, apathy, and the terminal deliriums are probably in a measure dependent upon these lesions, the chief agent is probably some toxin. Various attacks of cortical origin, as convulsive seizures and transient hemiplegic attacks, have been described.

Defects of the special senses, dependent upon changes in the central nervous system, are rare, the commonest being optic atrophy and optic neuritis. Defects of sight, however, are fairly common, some evidently dependent upon the anemia per se, as are certain auditory disturbances such as buzzing in the ears; but others are dependent upon retinal hemorrhages. The great frequency of these was first noted by De Schweinitz[81]. They, however, often give no noticeable symptoms. Hemorrhages may, also, occur in the ears. Such hemorrhages occur usually late and not early in the disease and will be referred to again when discussing other forms of hemorrhages that may occur in the disease and the diminution of the blood platelets upon which they may depend.

Miscellaneous Symptoms and Signs

The important features of the disease have been outlined above, except those important ones rather definitely referable to blood destruction and blood formation, but before discussing these a brief résumé will be made of the other remaining symptoms and signs that may develop in individuals with pernicious anemia.

Symptoms, as muscular weakness, dyspnea, palpitation, vertigo, fainting, simply dependent upon the anemia itself will of course occur. Edema may also develop, particularly in the feet, but also in the hands and sometimes the face; likewise serous effusions in the pleural cavity are not uncommon, but ascites is distinctly rare. In some instances, these accumulations of fluid are dependent upon an incompetent myocardium, while in other instances their physiological cause is unknown but may be the result of a compensation for a diminished blood volume.

Symptoms referable to the circulatory apparatus are sometimes the first ones of which the patient complains, but when such is the case, other features of the disease will be present; though not uncommonly one finds that the diagnosis of a primary cardiac condition has been made. The heart shows fatty degeneration and presents a tiger-lily-like appearance. Actual cardiac hypertrophy, sometimes of a very considerable degree, is often associated with pernicious anemia, as Cabot and Richardson[82] have pointed out. The physical signs of the heart are those common to anemia and myocardial weakness, so the presence of soft systolic murmurs is the rule. Diastolic murmurs evidently dependent upon dilation of the aortic valve may also occur. The blood pressure is usually low. Like other severe anemias, signs dependent upon relaxation of the vessels may be present, as marked pulsation of the carotids, collapsing and even capillary pulse, and venous hums. Some such phenomena may well be dependent upon a diminished blood volume.

It may be noted here that it is rather characteristic in this form of anemia to find that an individual at one time may perform laborious tasks in the face of a severe grade of anemia without experiencing symptoms dependent upon it, including gastrointestinal symptoms, while at another time with the same grade of anemia, he will experience such symptoms. Lindeman[69, 70] has pointed out that this state of affairs is dependent upon blood volume, it being normal or perhaps increased in the former instance, and diminished in the second. At times when the blood findings are misleading, one may lean toward the diagnosis of pernicious anemia rather than some other type of anemia, except perhaps hemolytic jaundice, because the individual seems surprisingly well in spite of the grade of anemia present.

The renal function in patients with pernicious anemia, as has been particularly pointed out by Mosenthal[83] and Christian[84], is frequently impaired. It is similar to that found in patients with advanced chronic nephritis, but the disturbance appears to be due to the anemia, as it decreases with subsidence of the severity of the anemia and is probably not dependent upon actual renal lesions. Thus of course small amounts of albumin and casts are commonly found, and in a similar way as cases of pernicious anemia are wrongly diagnosed heart disease, they are not infrequently wrongly diagnosed chronic nephritis.

Slight acidosis not infrequently occurs in cases of pernicious anemia and may cause accentuation of certain symptoms.

The relation of sepsis to the disease is probably frequently exaggerated and we must not forget that we may have a severe anemia resulting from sepsis alone. Sepsis is, however, an undesirable complication of pernicious anemia. Sepsis may well be such a handicap to the patient in general, as well as because of its ability to depress the marrow or increase red cell destruction, that it hinders improvement. Consequently if sepsis is present, it is desirable to remove it if reasonably possible. The commonest form of sepsis found in these cases is that associated with the teeth. Pyelitis is also not an infrequent complication, and gall bladder infections may occur as well as other local septic conditions.

(*d*) *Features of Pernicious Anemia Dependent upon or Associated with Abnormal Red Cell Destruction*

There are certain features of the disease that are dependent upon, or at least associated with, the abnormal red cell destruction, such as the color of the patient, changes in the liver and spleen, fever and increased amounts of blood-derived pigments in the plasma and excreta.

Color of the Patient.—The typical lemon color of the skin and conjunctivae presented by cases of pernicious anemia is an expression of the hemolytic process that occurs in the disease. As usually this is not marked early in the disease; the color seldom is the first thing that attracts the patient's attention to the fact that he is not well, though it may do so in some instances. The same is true of the pallor itself. This type of jaundice, hemolytic in nature, though a feature of pernicious anemia, occurs of course in other anemias associated with distinct hemolysis. The amount of this color is roughly a measure of the degree of blood destruction that is occurring, but it is far from being as accurate an indicator of this as other features mentioned below, for its absence does not preclude by any means a definite degree of increased hemolysis. Of course a change of color, a paleness, is a feature of the anemia, but when there is an excessive hemolysis, as particularly occurs with relapses, an added yellow color appears. The ease with which this yellow color will be observed depends not only on the degree of blood destruction but probably upon the degree of saturation of the tissues with pigment. Sometimes the color is intense enough to be called an outspoken jaundice. Great increase in intensity of the yellow color may develop very rapidly in even a few hours. In many cases the yellow color is not definitely apparent, though rarely do individuals appear with simply an intense whitish pallor. Contrasted with other chronic severe anemias having this color pernicious anemia patients usually present a good preservation of the subcutaneous fat layer. Another change in color that may occur in pernicious anemia is a brownish color of the skin. In some instances this undoubtedly is dependent upon arsenic which is commonly given these patients. In other cases, no such association is found. It is apt to be found more commonly on the unexposed parts of the body and on the mucosae of the mouth. However, it may occur only on the exposed parts of the body not due to sunburn, and the question arises whether in some instances this pigmentation might not be dependent upon a photodynamic effect of the abnormal amounts of blood pigments present, as Sellards[85] has suggested.

The Spleen and Liver.- The spleen, as has been discussed by Drinker (Chap. XV), is intimately related to increased blood destruction. Its size, however, does not tell us the degree of this at any one time, and no gross abnormal hemolytic activity of the pernicious anemia spleen can be demonstrated by the action of its juices, as Robertson[86] and others have shown. In pernicious anemia the spleen[14] shows a great richness in blood, predominately in the pulp areas in contact with the connective tissue spaces, the sinuses being comparatively empty. It is supposed that it is here that some hemolysis occurs and that phagocytosis of the red cells in the spleen also plays a part. Some hemolysis, also, probably occurs in the liver, particularly in the Kupffer cells of the parenchyma and it may occur in other parts of the body. As a result of the hemolysis, the excess of liberated pigment is stored in the body, particularly in the liver and spleen.

The spleen, in about 40 per cent. of the cases, is enlarged so that it is palpable; usually it is but slightly enlarged so that it is only just palpable, but rarely one finds it enlarged to the umbilicus. It is possible that the pernicious anemia cases with these distinctly larger spleens belong to a somewhat different type of anemia.

The liver in a slightly higher percentage of cases will be found to be slightly enlarged, not due to cirrhosis of the liver or passive congestion, etc., but to pernicious anemia. Sometimes one organ alone is enlarged, usually the liver, but more commonly both are enlarged together. This enlargement of the spleen and liver is greater later than earlier in the course of the disease, probably because it is dependent upon hemolysis. In fact, it seems that it is in the cases with the greatest hemolysis that these organs are the largest. Likewise, we[61] have noted that as a rule cases with the larger spleens and livers have run a more favorable course of their disease after it is well established than those without such enlargements. This is the same as saying that the more hemolytic cases run a more favorable course than the more myelotoxic cases.

Kahn and Barsky[87] have noted that glycogenic and urogenic functions of the liver are usually normal, but that the detoxifying function is somewhat deficient.

Fever.—Fever is of common occurrence, and its presence is usually coincident with periods of excessive hemolysis, that is in relapses; but it should be noted that some cases with apparently the same degree of hemolysis do not have the same amount of fever. It is not present during remissions. Its exact cause is not known, but its presence indicates a relatively severe stage of the disease. As a rule the fever is irregular and of a low grade, but at times sharp daily swings of three or four degrees Fahrenheit may occur; at other times a sustained temperature of several degrees may be present. Such types of fever may be present for many weeks at a time. The onset of fever may be gradual or abrupt. Subnormal temperature is also not uncommonly seen.

Laboratory Evidence of Blood Destruction.—The patient's color, the size of the spleen and liver, and the duration of such enlargements, as well as perhaps the presence of fever, are the clinical observations that tell us something about one of the factors that go to make up the anemia, namely blood destruction. Other symptoms and signs may well be more pronounced when this is more active, but certain data obtained in the laboratory will give us the best information about blood destruction. This will be referred to first before discussing the other important factor that causes the anemia, namely, abnormal blood formation. It is evident from what has been said previously that we must consider the balance between these two factors in a given case in order to understand the condition of the patient.

Blood destruction will be found to be greater when the individuals are doing poorly and be less as improvement occurs, while removal of the spleen causes the blood destruction to become lessened. Though two individuals may have the same degree of blood destruction, one may have greater activity of formation than the other, so that one may improve in spite of the destruction, while the other does not. The laboratory evidence of abnormal blood destruction as determined by abnormalities of the blood pigment metabolism is plentiful, and such determinations are valuable not only to tell the state of a given patient but also are serviceable to aid in the diagnosis of the disease. Those wishing full information regarding the blood pigment metabolism are referred to the articles by Addis[88] and Whipple and Hooper[89].

The urobilin excretion as determined in the feces and urine is frequently found to be much increased, often being normal during the height of good remissions. By Wilbur and Addis'[90] method read by the spectroscope in terms of dilution of the total 24-hourly stool, the urobilin is normally not over 9,000, while in pernicious anemia, it not infrequently reaches 30,000 [91, 92, 93], while the highest figures of all occur in chronic hemolytic jaundice, indicating the marked degree of blood destruction that occurs in these cases. The urobilin excretion as expressed in grams as given by Eppinger[44] is normally 0.15 and in pernicious anemia may reach 1.15. Schneider[94, 95] and others[87, 96] have estimated the amount of hemolysis by the examination of the duodenal contents, and have found excessive excretion of bile pigments. Schneider considers that a pleochromie or excessive excretion of bilirubin is an expression of immediate hemolysis and is a constant finding in pernicious anemia, whether in crises or remissions. This point has not as yet been studied sufficiently for all to be agreed.

Schneider[94, 95] also finds, as have others, a urobilinocholie and an increase of urobilin and urobilinogen in the duodenal contents. This is considered as an expression of the heaped up pigment in the portal system and varies probably directly as there is an added excessive hemolysis or not, so that it is approximately proportional to the urobilin in the stool. When active erythrocytic destruction is taking place, it is natural to expect that the limit must be approached above which the liver and other tissues can no longer dispose of the liberated pigment. That such may actually be the case has been suggested by Sellards and Minot[97]. They found that, compared to normal, a smaller intravenous injection of hemoglobin is required to produce hemoglobinuria in cases of pernicious anemia and other instances where blood destruction is excessive than in normal cases or cases of simple anemia of an equal grade but without excessive blood destruction. In some instances of pernicious anemia an actual spontaneous hemoglobinuria may occur, as Laache[98] was the first to observe. Of course the presence of hemoglobin in the urine would indicate a most unusually rapid liberation of the blood pigment. Slight degrees of this may be found more often than is usually recognized if the urine is critically and properly studied with the spectroscope.

Dependent upon the fact that there is an excessive liberation of iron in the system, a siderosis of the kidney occurs as it does in the liver. This may result in the frequent finding of urinary sediment cells filled with quantities of hemosiderin as shown by Rous[99] and alluded to by Ward[11]. The presence of these may be of service in the recognition of pernicious anemia as well as in other conditions in which siderosis occurs.

Though urobilin and urobilinogen are the blood derived pigments which are found in excessive amounts in the feces and urine in pernicious anemia, they are not the ones found in the plasma. In the plasma excesses of bilirubin are found such as occur in duodenal contents, while the true bile pigments are not found in the urine. Hannema[100] has discussed the value of finding bile pigments in the plasma as an aid to diagnosis, as well as from other aspects. Cases showing high concentration of bilirubin in the plasma are those that show other evidences of rapid blood destruction, as has been shown by Blankenhorn[76] and the author. A crude but useful method for the determination of the amount of bilirubin in the plasma, and thus the simplest method of obtaining a figure for the degree of blood destruction provided no biliary obstruction is present, is simply to observe the jaundiced color of the plasma and find the amount that it may be diluted before the color goes. As a method of prognosis, this method of measuring the blood destruction will be found serviceable, for a decrease of the jaundice of the plasma is associated with relief from symptoms and is usually associated with increase of red cells, because lessening of destruction usually occurs with elevation of the red cell level. It is not to be lost sight of, however, that it seems that considerable blood destruction may occur without the color of the plasma being significantly abnormal, so that lack of increased yellow color of the plasma is not to be taken to indicate lack of abnormal blood destruction, though no marked degree will occur in pernicious anemia without a considerable jaundice of the plasma. It might be thought that the degree of jaundice observed in the plasma would be proportional to the color of the patient, but this is not so, and it has been alluded to before, that absence of the yellow appearance of the patient does not preclude the presence of considerable increased blood destruction. When cases do appear yellowish, there will always be abnormal jaundice of the plasma, but the converse is not true. We agree with Blankenhorn[76] that a distinctly jaundiced plasma is frequently observed in cases of pernicious anemia that do not appear yellowish. Though a considerable concentration of bile pigments often occurs in the plasma, as do the true bile salts, rarely do either appear in the urine.

A further way of obtaining insight into the degree of blood destruction present may be found in the histological examination of the blood, as Drinker (Chap. XV), has referred to. This may be done by judging, particularly in fresh preparations, the frequency of microcytes, tailed cells, and other red cells that appear to be fragments of cells, or cells actually in the process of fragmentation. Rous and Robertson[101, 102] have recently discussed such cells, and by their special methods their frequency may be more readily demonstrated. Of course some abnormally shaped small cells may be due to a defective formation. It may be noted that we[103] have associated microreticulated cells and reticulated cells with filamentous processes, etc., with increased erythropoiesis in the presence of considerable increased erythrocytic destruction.

(*e*) *The Abnormal Blood Formation in Pernicious Anemia*

It is characteristic of the disease to have an abnormal blood formation in contrast to the relatively normal type formation seen with simple chronic anemia, and it may well be that abnormality of blood formation is the primary feature of the disease, and that the excessive destruction is in some way secondary to this process. The pathology of the marrow has not been studied as much as one might wish. Future studies may decide whether or not there is any absolutely distinctive feature of it that is associated only with idiopathic pernicious anemia. The marrow does, however, show changes that are fairly distinctive of the disease but which in general may be reproduced in other conditions, as well as experimentally by ricin, as Bunting[54] has shown, but such changes are relatively seldom seen in man except in pernicious anemia. The marrow throughout is red, the fat being replaced by hyperplastic tissue. Extensive proliferative activity is evident, but from the course of the disease the activity evidently progresses to an abnormal type that cannot accomplish the desired result. The erythroblastic cells occur in groups or islands in which megaloblasts are conspicuous. The proliferation of the red cells would appear to crowd out the leukocyte forming elements and the megakaryocytes from which the platelets are formed, evidence of which is reflected in the peripheral blood picture. However, there will often appear in the marrow extensive formation of hematoblasts and their derivatives. Phagocytic cells loaded with red cells, their shadows and fragments are found, so that some of the process of blood destruction may occur in the marrow. Occasionally erythropoiesis may occur in the liver and spleen, as Drinker has referred to in the previous chapter.

The ability of the marrow to perform its function is reflected in the peripheral blood picture. It is important to judge the activity of the marrow as well as the degree of blood destruction, in order to understand the state of the patient. The histological findings as well as the hemoglobin content will be discussed not only from this point of view but from that of diagnosis.

One must realize that the histological blood changes are to be looked upon as a sign and not as an absolutely pathognomonic feature of the disease, in a similar way as fine crackling râles at a lung apex do not mean necessarily tuberculosis. It is true, however, that the fully developed typical blood picture about to be described, is vastly more commonly seen in pernicious anemia than in any other disease, although apparently it may occur due to certain other conditions later to be described. These conditions are much more apt to simulate the less typical blood picture than the fully developed one. The chief features of the typical fully developed blood picture are a high color index with a marked macrocytosis including many oval or abnormally shaped, deeply staining, large macrocytes in the presence of fragmenting cells and microcytes, megaloblasts, leukopenia and diminished platelets.

Red Count.—As Cabot[13] has aptly said, there is no other disease which so often reduces the erythrocytes below 2,000,000, and it is a surprising fact how frequently the count will reach this level before an individual feels sick enough to consult a physician. The count may go below 500,000 and a marked remission still occur. The rate at which the count falls varies greatly. It would seem as if it fell relatively more rapidly between 5,000,000 and 3,000,000 than between 2,000,000 and 1,000,000 and rose in like proportion. Though it usually takes the count over six months to fall from 5,000,000 to 2,000,000 such a fall may occur in a matter of days. Increases in the count likewise may occur slowly or rapidly; we have seen a count rise after transfusion of 500 c.c. of blood from 400,000 to 3,000,000 in three weeks' time. However, once the red count has fallen, it is rare to find it 5,000,000 again, though in some instances it may reach 6,000,000. On the average in good remissions, when the individual feels, as he states, practically perfectly well and frequently looks so, the red count will be but a little over 3,000,000. It is important to emphasize that a change in count may mean not only a change in the total number of red cells dependent upon increased formation and lessened hemolytic activity, but also upon a change in the blood volume. Likewise it is to be noted that the counts at least below 3,000,000 bear no relation to the symptoms, and that individuals may die with red counts which they had at other times when they were relatively symptomless.

Observations upon the *hemoglobin* content of blood in the past have been notoriously unreliable, and it is but recently that new and accurate methods [104, 105, 106, 107] have been developed which may well cause us to change our views regarding certain features of blood conditions. However, it is evident that in pernicious anemia the hemoglobin remains relatively higher than the red count so that the color index is one or above. The appearance of the cells is a better measure of the color index than if determined by the usually inaccurate hemoglobinometers and the routine red counts. Capps[108] has considered that increased volume index explains the high color index. With improvement one associates a falling color index and with relapse a rising index; exceptions however occur.

Grossly the blood often looks as red as normal because of the high color index. In severe cases it is often very watery and frequently leaves a pale ring about a red spot on blotting paper, seldom seen in other anemias. Because of increase of pigments in the plasma and at times hemoglobinemia a peculiar color may occur.

The red cells may show practically any of the abnormalities of these cells that are known to occur except a definite degree of achromia. A large percentage of deeply staining macrocytes, as well as very large macrocytes, is a particular feature of pernicious anemia. It is at least exceedingly rare that other conditions give such a marked degree of macrocytosis as commonly occurs in pernicious anemia. The presence of large, at times enormous, oval or abnormally shaped, deeply staining red cells is a distinctive feature of the disease, and the presence of such cells alone will be suggestive of the disease. Simple round macrocytes may occur but these *alone* much more commonly occur in other conditions. Not only do occasional oval macrocytes occur but there is a definite tendency for many of the cells to be oval. Marked degrees of macrocytosis and ovality are apt to be associated with poor health, but macrocytosis may be slight with low red counts and, in some, blast crisis. Cells smaller than normal and tiny microcytes are also commonly seen, so that distinctly marked variation in size often occurs. All forms of abnormal shapes may occur, the most bizarre particularly occurring among the medium sized and smaller cells, but it is to be noted that we believe narrow, long round-ended cells are much more commonly seen in simple chronic anemia, and the presence alone of many such cells should favor this diagnosis rather than pernicious anemia. The presence of many microcytes and fragmented cells probably indicates a considerable degree of increased destruction. Hence marked degrees of poikylocytosis are to be associated with at least a temporarily poor prognosis unless other factors indicate lessening of destruction and increase of an orderly regeneration.

The typical red cell picture is easily recognized, but when cases are seen early or at the time of a good remission, it is much more difficult to judge the significance of the findings. The red cell picture with such a stage of the disease at a first glance often appears not significantly abnormal, but we believe that once a patient has had a relapse, abnormality of the red cells will always be found that should suggest pernicious anemia. However, in the presence of a high red count the occasional finding of a typical large oval cell, especially with a tendency to macrocytosis and ovality, though slight, with an occasional microcyte or fragmented cell, is to be looked upon as suggestive of the disease. Though usually the more the red cells approach normal in their characters the better is the patient, it must not be forgotten that it is not from these elements alone that one judges the state of the marrow or the condition of the patient. Likewise, though relatively normal sizes and shapes are more usual with a better than a poorer state of the patient, one must recall that if the marrow is depressed or sluggish or a secondary aplasia ensues, the cells may be relatively less abnormal in size or shape. It is thus important to take into consideration the level of the anemia at which a given red cell picture is found. The presence of signs of youth and regeneration of the red cells is commonly seen in this disease, as evidenced by some increase of the reticulated red cells and the like. It would seem that when the reticulation was present, particularly in large cells alone, that it was not as desirable a sign of active regeneration as when it, also, occurred rather plentifully in the more normal sized or smaller cells. Reticulation of microcytes and hemoglobinless reticulated cells may be associated with destruction of young cells as similar bodies noted by Rous and Robertson[101, 102] are associated with destruction. The percentage of reticulated cells is frequently found to be 1 to 2 per cent. and regeneration may proceed slowly without a further definite increase. On the other hand, at times of active rapid regeneration, they may become much more numerous, 15 per cent. or more. Unlike in hemolytic jaundice they are not always considerably increased. When the individual's blood is at a high level, they may be diminished below normal and be distinctly rare. Such a state of affairs is not to be confounded with aplasia. Robertson's[109] work on artificial plethora is interesting in this connection.

Light polychromatophilia and fine stippling frequently occur and run roughly proportional to the reticulated cells. Dense polychromatophilia, particularly of the larger cells which commonly show this, and coarse stippling are not to be looked upon as desirable findings.

Nucleated cells of all types are common in pernicious anemia. Megaloblasts in the past have often been considered as necessary for the diagnosis of this disease. It is to be noted that this is by no means so and that these elements in the peripheral blood simply represent a physiological condition (see Drinker, page 513), a condition in which there is a severe demand upon the marrow to supply new cells. It is true, however, that megaloblasts are more commonly seen in pernicious anemia than in any other disease except myelogenous leukemia, and that their presence, as well as that of the more mature nucleated red cells, normoblasts, favors a diagnosis of pernicious anemia. In fact, probably all cases have blasts at some time in the course of the disease, but their numbers may vary considerably from day to day. It would seem as if the spleen had some regulatory function over the marrow and that one of the effects of its removal was to lower the marrow threshold as evidenced, among other findings, by the quite constant occurrence of blasts even with high red counts. Thus a considerable number of blasts following splenectomy in pernicious anemia is not to be viewed with the same aspect as in cases where the spleen is present.

Blast crises, with which are associated numbers of other immature bone marrow cells, are an interesting feature that may occur in this disease; they represent a great effort on the part of the marrow to regenerate. As a result marked blast crises are more apt to be followed by further relapses than by improvement. Not infrequently such crises, with a pouring forth of all sorts of hematoblasts, occur just before death; the crisis seems to be the marrow's last final effort and one which results in a practical dissolution of the marrow. At other times a shower of blasts, more often of moderate or slight degree, often precedes a remission which may be transitory and slight. With the presence of many blasts, there is inevitably associated an increase of the reticulated cells; when they are proportional to the number of nucleated cells a very severe effort at regeneration is occurring which is apt not to meet with success. When the young red cells are increased out of all proportion to the blasts, an intense increased activity of the marrow is occurring which will probably succeed in improving the patient.

Further evidence of a severe effort at regeneration is seen by the presence in the erythrocytes of nuclear remains, as Cabot's ring bodies, chromatin particles and perhaps Howell-Jolly's bodies. The presence of the latter structures in the peripheral blood is especially associated with altered splenic function and particularly occurs after removal of the spleen. When Howell-Jolly's bodies are present they do not necessarily vary with the presence of even many blasts.

The white cells typically show a leukopenia, the polynuclear percentage remaining about normal. This feature of the blood is simply further evidence of marrow deficiency. Absolute diminution of the polynuclears with relative lymphocytosis is also not infrequently found, indicating of course still greater marrow deficiency. The lymphocytes are usually all small and it would seem as if large lymphocytes were more apt to be found only when the cases were doing relatively well. With remissions the marrow functions more normally, the absolute count of the polynuclears rises and, with the lower threshold resulting from removal of the spleen, the white count constantly remains at a higher level than when an individual is in a similar state with his spleen intact. Considerable information concerning the state of the marrow activity is, of course, to be found in observing the white count over periods of time, but it must be recalled that complications and slight influences may cause it to vary somewhat from day to day, and it is only by its general trend rather than by isolated observations that one obtains the best information from it. Evidence of the depressed state of the white cell portion of the marrow in pernicious anemia is, also, to be seen in the slight response of the marrow to infectious processes causing leukocytosis and to injections of such substances, as nuclein[110, 111], that cause the same.

It is a rather characteristic feature of pernicious anemia blood, as has been noted by Briggs[112], to find the Arneth count of the polynuclears considerably to the right, which means that there are many cells with abnormally large number of lobulations to each nucleus. This indicates that cells are old and is further evidence of poor marrow activity.

When the marrow is working hard to form blood and is not succeeding well, it may be reflected in the peripheral blood picture of the white cells by the not infrequent finding of a few myelocytes which may reach 10 per cent., as well as by the presence of various atypical mononuclear cells of bone marrow origin. Such are, of course, particularly prone to occur with blast crises. In this connection, it is to be noted that with a great outpouring of immature marrow white cells and blasts, the white count may be even 50,000 and it may cause one incorrectly to diagnose the condition as one of leukemia.

The eosinophil cells are commonly normal in number. The presence of them, and particularly increases of them, are to be looked upon as a desirable sign, because the patient is apt to improve following a period of definite increases of these cells. Absence of these cells does not indicate a distinctly undesirable feature, but it would be one small point that would be placed against the chances of improvement. No abnormalities of significance have been noted of the other white cells.

The blood platelets give still further evidence of the depressed activity of the marrow, for it is typical to find a diminished number of them. The platelets are particularly significant for they seem to be the best single indicator of the activity of the marrow[61] in this disease, for no considerable improvements occur unless they show a definite, not purely transitory increase. The other marrow elements may increase considerably and the platelets slightly or not at all, but then only a slight improvement would occur. Like the leukocyte count, the number of platelets tends in general to follow the curve of the red cells in the usual course of the disease. Though the platelets may reach normal numbers during marked remissions and very rarely actually become increased, it is to be noted that even with the higher red counts they will not infrequently be somewhat diminished. This fact alone, but particularly when taken with symptoms and other blood findings, is a point in favor of the diagnosis, for in most other anemias at a relatively high level of the hemoglobin and red cells the platelets will be found increased. It is not to be forgotten that there are other important conditions, especially purpura hemorrhagica, in which the platelets may be markedly decreased and the red count relatively high.

With the altered threshold resulting from the removal of the spleen[103] the platelets often became markedly increased to well above normal, and they will remain, with fluctuations, at a considerably higher level in such individuals than in those whose spleens have not been removed. We have associated abnormally large platelets with such a lowered threshold, and the considerable number of such following splenectomy is striking.

Very marked decrease in the number of platelets indicates failure of the marrow and is an ominous sign, and though remissions may occur following such a finding, a remission is relatively unusual. Associated with this deficiency we have a symptomatic purpura hemorrhagica, so that the presence of a few petechiae, slight bleeding about the gums and slight nose bleeds, is not rare and when such occurs it is to be looked upon seriously though remissions may occur following such symptoms. More marked evidences of purpura are unusual, though hemorrhages from any part and in considerable amounts may occur. Hemorrhage, however, in rare cases may be the first sign that attracts the patient's attention to his disease.

From what has been stated about blood formation and destruction, one may see how it is necessary to take into consideration numerous features in order to judge the patient's condition at any one time as well as for diagnosis of the disease.

(*f*) *Coagulation of the Blood*

The coagulation of the blood in pernicious anemia is not greatly altered. Drinker and Hurwitz[113] and Minot, Denny and Davis[114] have studied this. The coagulation time and prothrombin time are slightly delayed. This may also occur in other anemias with diminished activity of the bone marrow.

(*g*) *Fragility of the Red Cells*

Of the other numerous blood studies that have been made in pernicious anemia, we will refer to but one, namely, the fragility of the red cells[115, 116, 117, 118, 119] to various strengths of salt solution. This test frequently shows no abnormality but in other instances the fragility will be found markedly decreased, that is, an increased resistance. Following removal of the spleen an increased resistance occurs. This is in contrast to the decreased resistance seen in hemolytic jaundice, though it is to be noted that rarely cases of pernicious anemia may show a slightly decreased resistence. By means of this fragility test certain studies we have made suggest that it may give us some information regarding the state of the blood forming organs in this disease.

Differential Diagnosis of Pernicious Anemia

Most cases of pernicious anemia will be readily diagnosed if one keeps in mind first the clinical symptomatology of this disease, including the fact that tongue symptoms and symptoms referable to the central nervous system are common and achylia is the rule. Secondly, one must recall that increased red cell destruction is a feature, that a rather characteristic abnormal blood formation occurs, which is reflected in the peripheral blood picture, and that variations in the activity of red cell destruction and blood formation permit the characteristic feature of relapse and remissions. Though the characteristic blood picture of pernicious anemia is seen vastly more often in pernicious anemia than in any other condition, it must not be lost sight of that it can occur in other conditions, as referred to in this section on pages 636, 642, and also one must remember that cases of pernicious anemia occur without the typical blood picture.

Before diagnosing a case as one of pernicious anemia, it is of course important to exclude other forms of anemia. The anemias taken up under "Other Anemias than Pernicious Anemia in which the Hemolytic Factors play an Important Role" are discussed from this point of view, including chronic hemolytic jaundice which is further referred to in the section on Diseases of the Spleen, Vol. IV, by Sailer. Chlorosis and idiopathic aplastic anemia should be readily distinguished from pernicious anemia from what has been said about these conditions. The severer anemias of the simple chronic type, particularly those due to intestinal parasites, malignancy, syphilis, etc., and those following acute and chronic hemorrhage, are to be distinguished from pernicious anemia. This is done first by the presence of a recognized cause and by the absence of symptoms and signs suggesting pernicious anemia, and, secondly, by the absence of any important degree of red cell destruction and by differences in the histological blood pictures which have been described. The chief differences in the histological blood picture are a lower color index than in pernicious anemia, the absence of macrocytosis and the frequent increases of platelets and bone marrow white cells.

Those conditions such as Banti's Disease particularly discussed under Diseases of the Spleen, Vol. IV, by Sailer, are also to be excluded. The large size of the spleen alone in these conditions will usually, but not always, serve to rule out pernicious anemia, while the absence of the clinical features of pernicious anemia and the pernicious anemia blood picture are important points in the differential diagnosis. Krumbhaar[120] in 1915 discussed very fully the conditions with enlarged spleens and their differential diagnosis.

Heart disease, arteriosclerosis, and kidney disease, may be wrongly diagnosed when the condition is pernicious anemia, as may Addison's disease; but from what has been said regarding the patient's symptoms, these conditions are usually readily ruled out and they do not have the blood disturbances seen in pernicious anemia.

The presence of fever due to pernicious anemia may lead to the diagnosis of endocarditis, tuberculosis and even typhoid, and one must remember that fever is a frequent occurrence with pernicious anemia.

The spinal cord disturbances should not be confused with disease of the central nervous system due to syphilis or multiple sclerosis, while the gastrointestinal disturbances must not allow one to be led to the diagnosis of some purely gastrointestinal disease.

There is one condition that may be, as a rarity, quite difficult to distinguish from pernicious anemia, and this is myxedema. This is because as a rarity the histological blood findings may be quite like those of pernicious anemia of a myelotoxic type, and the insidious onset of the disease may be like it. However, the anemia present in myxedema is usually of the simple chronic type, and a careful study of the patient, including the finding of a much diminished basal metabolism will distinguish the two conditions. In this connection it is interesting to note that certain definite cases of pernicious anemia may exhibit certain signs of myxedema, as coarse hair, dry skin, lethargy, etc. What relation exists in such instances between the thyroid gland and the anemia, as well as in those cases of marked myxedema with pernicious anemia histological blood findings and depressed marrow activity, is interesting and problematical.

(2) OTHER ANEMIAS THAN PERNICIOUS ANEMIA IN WHICH THE HEMOLYTIC FACTORS PLAY AN IMPORTANT ROLE

In the anemias in which the hemolytic factors play an important role, we find all the distinct evidences of increased blood destruction as discussed under pernicious anemia, so that the sclerae are yellowish and the spleen commonly is enlarged, being larger in the more hemolytic and more chronic conditions. Though enlargement of the spleen usually occurs when there is increased red cell destruction, marked enlargement of this organ in anemia does not by any means necessarily indicate that marked blood destruction has occurred or is occurring. For example, the large spleen of Banti's disease is associated with little if any blood destruction. Fever may be present in these hemolytic anemias, but marked degrees of blood destruction may occur, as in chronic hemolytic jaundice, without fever. With extraordinarily rapid hemolysis, many fragments of red cells may be seen in the peripheral blood, while poikilocytosis and microcyte formation is frequently marked. An increased fragility of the red cells to various strengths of salt solution is characteristic of the purer forms of hemolytic anemia.

In some of the conditions referred to in this section, it would seem that the marrow was more or less deeply implicated in the production of the anemia and such cases perhaps may well be classed separately. The instances where the marrow seems rather deeply implicated are ill-defined cases of chronic hemolytic anemia and some of the cases due to chronic sepsis, malignancy, syphilis, fish tapeworm, occasionally pregnancy and certain acute cases caused by poisons. In this group of cases the evidences of blood destruction, both clinically and from laboratory tests, are often much less marked than in the purer forms of hemolytic anemia, such as chronic hemolytic jaundice and many cases of acute hemolytic anemia. In these conditions of purer hemolytic anemia, though hemolysis is usually marked, the marrow does not seem deeply implicated in the production of the anemia as shown by a constant active response of the marrow.

In the purer hemolytic anemias the products of blood destruction, together with a probable increased oxygen want, permit increased activity of all the marrow elements. This may become so marked that there will occur an outpouring of nucleated red cells and other immature cells from the marrow. Though hemolysis may keep up for years and the marrow respond well, as in congenital hemolytic jaundice, in other instances of hemolytic anemia, both acute and chronic, the marrow early or later, may become depressed. Evidence of this is first seen in the white cells or platelets and later in the red cells. An actual aplasia may result from a condition that at first allowed considerable augmentation of the marrow activity, though this may not be dependent upon the hemolysis as such, but upon some other factor acting directly on the marrow.

One finds in most text-books the statement that this group of anemias may give the blood picture of pernicious anemia. Such may be the case in that the picture they present may be seen in pernicious anemia at some stage of a given patient's illness with that disease, but we believe that it is most distinctly rare to find instances other than pernicious anemia that give a marked general macrocytosis with large oval red cells. Macrocytes may occur and all the other features of the blood seen in pernicious anemia undoubtedly may be present to a marked degree in other conditions, but a marked general macrocytosis with oval red cells, decreased platelets and bone marrow white cells seems to be one almost, but not absolutely pathognomonic feature of pernicious anemia. A higher, rather than a lower color index, is apt to be a feature of hemolytic anemia, but, depending upon the state of the patient, it will vary and is not uncommonly found around 0.8 and sometimes lower, but never distinctly low. A picture simulating pernicious anemia may thus be seen on this account and particularly when the degree of anemia is marked.

Unlike pernicious anemia, many instances of the conditions referred to in this section recover or can be cured, and if so relapses do not follow. Likewise the cause of these conditions is usually recognized, except for the various forms of chronic hemolytic jaundice, which is in contrast to idiopathic pernicious anemia. A hemolytic jaundice occurs in all these conditions which may be chronic, but the term chronic hemolytic jaundice is reserved for a special disease with unknown etiology.

(*a*) *Acute Hemolytic Anemia*

The commonest cause of an anemia of this type is sepsis, particularly when due to streptococci. Other organisms can cause it, even the typhoid bacillus, as reported by Morusset, Mouriquand and Thevemot[121]. On account of the known cause, such cases are sometimes called acute septic anemia or acute febrile anemia. The anemia may develop with extreme rapidity, as Cabot[13] and Rideau, Dumas and Poisot[122] among others have noted, and I have seen this myself. The red count may drop to 1,000,000 in a few days so that one might be led to believe he was dealing with anemia from hemorrhage. Sepsis associated with childbirth and abortions is a type that particularly yields this condition, though in some such instances retained diseased placental tissue may play a part and this will be referred to again. With scarlet fever, among other conditions, such an anemia may develop.

On account of the fact that there may be a pouring out of many young marrow cells of all types in generous numbers in acute hemolytic anemia, the poor term of leukanemia has, in the past, been given to some such cases, in the belief that they were a cross between anemia and acute leukemia, but the presence of myelocytes and other immature marrow cells is of course only an expression of a tremendously rapid production in the marrow. Like other hemolytic anemias the color index will tend to be high. The red cells will show all variations in size and shape; evidence of regeneration and some macrocytosis is common. Rarely a rather marked macrocytosis may occur, but when this is present, unlike in pernicious anemia, commonly there will be increased platelets and white cells of bone marrow origin. In instances where the process is overwhelming or when such a process becomes subacute or chronic, evidence of decreased marrow activity may develop and an actual aplasia result. In septic conditions of a more chronic nature, a chronic hemolytic anemia may occur; a particularly good illustration of this is seen in malignant endocarditis. However, in such cases a marked exacerbation may occur, so that the picture of an acute hemolytic anemia may develop, which may later subside. Similar crises may occur in any hemolytic anemia.

In the course of general infections with the streptococcus viridans, acute or chronic, there not uncommonly occur considerable increases of true large endothelial phagocytes, which may be seen engulfing red cells, platelets, etc. Such a process may be an important one in the immediate cause of the blood destruction. We have seen instances like that reported by Rowley[123] and others[124, 125], where phagocytosis may be of an extreme degree with the white count over 100,000. Such cases have been called phagocytic anemia. Though severe acute hemolytic anemia due to sepsis is apt to prove fatal, the anemia may be even very severe and yet not be fatal as shown by Teeter's[126] case, among others.

In pneumonia a mild, rarely severe, form of hemolytic anemia may develop with altered fragility of the red cells.

Acute hemolytic anemia besides being dependent upon bacteria may be caused by malaria from the rapid destruction of the cells by the plasmodium, and in extensive burns an anemia of this general type may develop. Another interesting cause of this condition, summarized by Gasbarrini[127], is seen in Italy and known as favism, occurring more commonly in children than in adults. This results from the eating of fava beans or even from smelling their blossoms. In this condition marked evidence of blood destruction occurs, rather often including hemoglobinuria.

There are also numerous poisons that cause an acute hemolytic anemia, not only as shown by its production in animals but by poisoning in a man. Such an acute anemia can be produced by pyrodin[128], toluodiamin[129], phenylhydrazin, potassium chlorate, acetanalid and other coal tar derivatives, and other substances, including particularly the amido and nitro compounds of phenol, benzol and toluol, such as anilin, nitrobenzol and trinitrotoluol. Hamilton[130] has briefly summarized the blood findings in some of these poisonings.

The detailed different aspects of such poisonings will not be described, but it is to be pointed out that any of these poisons, as well as other conditions capable of producing an acute hemolytic anemia, may produce a chronic condition of this same type. There are certain features of the blood that will be mentioned briefly in regard to some such poisonings as occur in man. When such substances as the derivatives of anilin and the nitro compounds, referred to, cause an overwhelming intense poisoning and death in a few hours, methemoglobin formation will be the principal blood change observed. The more chronic the poisoning the less will be the evidence of this change, though it forms a characteristic feature. The evidence of blood destruction with active regeneration, often marked, will be seen in such poisonings, the degree varying with different substances. Apparently in some instances though rarely, if the process progresses, evidence of marrow depression, first exhibited in the white cells, then in the platelets, and later in the red cells, may occur, and an actual aplasia result.

A full account of the blood findings in one of these poisonings, that due to trinitrotoluol, has been discussed recently in full by Minot[131], and the alterations of the blood occurring with the related poisons are apparently similar. One of the features of the blood in trinitrotoluol poisoning is the frequent finding of definitely fragmented cells of a particular type indicating rapid red cell destruction. Entirely similar cells have been observed in acetanalid poisoning by Stengel and White[132]. These cells are usually about half the size of a normal red cell and stain darker than the other cells. They are irregular in one portion of their periphery and strands may be seen extending from them. At times a clear zone is seen between two split pieces or a pale zone appears as a cap to the darker portion. Shadow corpuscles may also be seen in processes where methemoglobin formation and rapid red cell destruction occur. Sometimes one may suspect from the blood picture that individuals are taking poisonous doses of coal tar products and the blood picture may lead to the diagnosis of such conditions when the patient has denied taking such drugs. This is because the presence of extreme variation in size of the cells, fragmented cells, many nucleated cells in severe cases, greatly increased numbers of platelets and usually increased number of leukocytes, are rather characteristic of the action of such poisons. Of course many cases do not develop so marked a picture, as this depends upon the rate and amount of the poison taken.

(*b*) *Chronic Hemolytic Anemia* *

1. *Chronic Hemolytic Jaundice.*—The acquired (Hayem-Widal) and congenital or familial (Chauffard-Minkowski) forms of the disease known as chronic hemolytic jaundice (chronic acholuric jaundice, chronic family jaundice, hemolytic splenomegaly) are the particular conditions in which the purest type of a chronic hemolytic anemia occurs. The cause of these conditions is unknown. It is, however, true that occasionally the acquired type may develop following attacks of malaria, syphilis and other infections, and sometimes removal of such an infection may clear the picture, but in many other instances the trap seems to be sprung so far that the condition persists. Chronic hemolytic jaundice is discussed in the chapter on Diseases of the Spleen, Vol. IV, by Sailer, and suffice it briefly to refer to it here because of the importance of distinguishing chronic hemolytic jaundice from other conditions with anemia.

In the typical and usual cases of hemolytic jaundice, there is evidence of a constant increased destruction of the red cells, usually of a greater degree than seen in pernicious anemia and present for years. The spleen is considerably enlarged, not infrequently reaching the umbilicus; definite jaundice without bile in the urine is present; fever is seldom seen except at times of considerable severity of the disease. With the constant increased destruction, there occurs a constant increased formation of red cells, evidenced particularly by the constant presence of increases, often marked increases, of the reticulated red cells which is in contrast to pernicious anemia. Also in contradistinction to this disease the color index is usually lower and the bone marrow usually acts much more normally in that the type of red cells produced is much more normal in character. Not infrequently the red cells are on the average, smaller than normal, and the cells larger than normal are round and not oval when they occur. Sometimes abnormally shaped macrocytes are found and a general macrocytosis may occur, but marked macrocytosis is unusual. Further activity of the marrow, which is in contrast to pernicious anemia, is seen in that the leukocytes are usually increased, as are the platelets. However, with the severer acquired types of hemolytic jaundice evidence of depression of the platelets and white cell elements may occur and together with macrocytosis the picture may be like that seen in typical pernicious anemia. A feature of the condition is the presence of an increased fragility of the red cells to various strengths of salt solution.

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* For a complete résumé of the literature and the experimental work on the spleen and anemia particularly in relation to hemolytic anemia, the reader is referred to Pearce, Krumbhaar and Frazier's[133] book on the spleen and anemia.

So long as the increased formation keeps balanced with the increased destruction, little anemia ensues. This state of affairs is much more frequent in the familial form of hemolytic jaundice than in the acquired type. Paroxysmal fluctuations in the degree of destruction occur, so that periods of greater anemia alternate with periods of fair health, and crises of increased activity of the marrow are not uncommon. Hence individuals with the milder types of the condition often have nothing to complain of but their color, and even with considerable anemia they frequently have little to complain of except of not feeling strong.

All grades of chronic hemolytic jaundice may occur. The severer cases of the acquired type may die of the disease, while the milder familial cases do not do so. There have been reported cases with the blood findings of idiopathic hemolytic jaundice which run a rather acute course and die in a few months. Variations from the typical picture of chronic hemolytic jaundice occur so that the blood may resemble pernicious anemia, and it would seem that the least compensated cases of the acquired type are in some way related to the more chronic hemolytic types of pernicious anemia, and it may be at times difficult to distinguish which condition is present. The absence of tongue symptoms and of symptoms referable to the central nervous system, as well as the increased fragility of the red cells and the large spleen, are features that lead to the diagnosis of hemolytic jaundice and not of pernicious anemia. The diagnosis from pernicious anemia should be made easily, at least in typical cases. It is important to do so because the prognosis in hemolytic jaundice is quite different from that in pernicious anemia, in that it is much more favorable. The therapy is distinctly different because splenectomy is to be urged in those cases of hemolytic jaundice ill enough to be handicapped by their condition. The results of this are often excellent, while in pernicious anemia splenectomy results in temporary improvement at the best, and is to be done only in certain selected cases.

2. *Ill-defined Chronic Hemolytic Anemia.*—As has been pointed out, acquired hemolytic jaundice may resemble pernicious anemia. Besides such atypical cases there occur other atypical hemolytic anemias, sometimes described as atypical instances of hemolytic jaundice and at other times as an idiopathic hemolytic anemia. For example, cases occur having all the features of chronic hemolytic jaundice but without enlarged spleen and others without visible jaundice, while instances of polycythemia with a very definite acholuric jaundice and enlarged spleen, with increased fragility of the red cells, have been reported. Besides such atypical cases we may see, and not so very rarely, patients whose illness appears to be chronic hemolytic jaundice in that they have had their difficulty for years with but little anemia. They appear very slightly jaundiced; slightly increased red cell destruction is present as is increased activity of the marrow, but no increased

blood disease rather than in those with a simple condition like anemia from blood loss. Some such reactions may be fatal. The cause of these is not clear, though some may be dependent upon a hemolytic condition due to the disease in the patient that acts on any blood. It does have to be recognized that, as a great rarity, unexplained serious reactions of a hemolytic-like nature have been reported following a first transfusion, when the bloods have been said to have been properly matched according to our present conceptions, and that such reactions seem particularly to occur in sick individuals with a serious blood disorder. In fact, it seems that not only the types of reactions referred to, but those shortly to be described, are more apt to occur in individuals with serious blood disease, than in those cases with relatively more normal hematopoietic organs. There is still a great deal of knowledge to be learned about the isoagglutinins and hemolysins, as well as the reactions following transfusion, though we can by proper tests and good operative technic avoid a very high percentage of serious reactions, and probably all very serious ones.

Besides the isohemolytic reactions and those that rarely occur, which resemble them but which are not fully explained, there are other reactions that may occur following transfusion of blood. These are of a milder nature. These reactions cannot be foretold and the exact cause of them is unknown. They consist of a sharp rise of temperature from a degree to four or five degrees and even more, with symptoms of fever and at times nausea, vomiting and diarrhea. The temperature usually falls to normal in a few hours; sometimes it falls by lysis in twenty-four hours or it may persist during several days. Chills may be associated with the temperature rise, and when these occur they usually appear about one hour after the blood has been given. At times the fever does not begin for eighteen hours, and then the temperature remains elevated for one to three days. Such a reaction may well be of a different nature from the others, and perhaps should not be spoken of as a transfusion reaction.

Urticaria sometimes occurs with these reactions with rapid rise of temperature, more rarely a petechial rash or some localized angioneurotic edema. Peculiar herpetiform vesicles may occur about the mouth. Reactions of this type, severe enough to be seriously alarming, are distinctly unusual.

These reactions may occur following the giving of blood by any method. However, they are much more common following the giving of citrated blood than blood containing no foreign substances. The percentage figures given for the frequency of these reactions vary greatly. It would seem that in round numbers, outspoken, rather marked reactions occur following the giving of whole blood in about 15 per cent. of the instances, and with citrated blood in about 35 per cent. of the instances, while a much larger percentage occurs if all temperature rises are included.

It seems that the less the blood is altered, the less chance is there of such reactions. It is to be noted, however, that such alterations are often beyond our control. It is well known that blood is a very labile substance and that outside the body important physical changes can occur in it which we do not understand and cannot appreciate. For example, at one time the transfused blood may appear in good condition and a reaction occur, while at another, the blood may be grossly partially clotted and no reaction occur. Even so, neat technic and the speed with which blood is transferred are all important, since under good technic with quick transference of blood fewer reactions will occur, as Lindeman[205] and others have stated.

Drinker and Brittingham[206] have studied these reactions with a view to finding their cause, and Satterlee and Hooker[207] have quite fully discussed this subject. These reactions are probably dependent upon different factors but the cause may be summed up by saying that they are probably dependent upon various alterations occurring with the initial changes of coagulation, such as slight changes in the blood platelets, that render the blood in a state similar to that of a foreign protein. The viscous metamorphosis of the platelets, as described by Wright and Minot[208], is an example of a change in the platelets that occurs during coagulation. Drinker and Brittingham[206] have suggested that a direct action of sodium citrate on the red cells that promotes hemolysis probably plays a part in these reactions that follow the giving of blood with citrate, and it is quite possible that similar changes may be induced when citrate is not present, though not so commonly. The susceptibility of patients to such reactions would appear to vary, as well as perhaps the ability of the donor's blood to produce such reactions.

It is not to be interpreted that because these reactions occur transfusion is to be postponed or avoided, for with proper tests and good technic, they very rarely will be of a serious nature.

(*c*) *Methods of Transfusion.*—Two general methods are available for giving blood from the vein of the donor into the vein of the patient: one, by giving blood mixed with an anticoagulant, preferably sodium citrate, early advocated by Lewisohn; the other, by giving blood to which no foreign substance has been added. The advantages of the citrate method are: it is simple, one man can do it; the blood can be collected at one place and given at another; relatively small injection needles can be used; skin incisions are rarely necessary. Also by the use of citrate, as Rous and Turner[209] and Robertson[210] have shown, red cells may be preserved and used for transfusion some two weeks after they have been collected. The disadvantages of the citrate method are that reactions occur in the patient more frequently than when pure blood is given.

The methods of giving pure blood, though simple, require rather more technic and experience than when citrate is used. It is very difficult for one person alone to transfer whole blood; relatively large injecting needles or cannulae are often required; often skin incisions in the patient with tying off of veins are necessary. The advantage of giving whole blood is that it will produce fewer reactions in the patient than citrated blood. Each method has its place, but when all possible disturbances to the patient are to be avoided, whole blood without citrate is to be preferred. When many transfusions are anticipated in a given case, the citrate method, requiring often less disturbance to donors and operative disturbance to patients, is to be preferred. When many transfusions are anticipated, the actual economic side of the question is often a very important one, so that the method causing the least trouble, time and expense to the patient is important.

The detailed technics for giving blood are numerous, and it is important to pay attention to details, as freshly prepared citrate solution, cleanliness of apparatus, etc. We cannot discuss here the different detailed technics, but will simply outline briefly three methods. Sterile precautions are of course to be observed throughout any of the procedures.

Technic of Transfusion with Citrated Blood.—A suitable method for giving citrated blood is as follows:

A high grade specimen of sodium citrate should be used. This salt will permanently suspend coagulation in carefully drawn blood in strength of 0.2 per cent. Owing to the fact that withdrawal by means of venepuncture is rather a slow way of obtaining blood, it is always advisable to increase the final strength of citrate to above 0.25 per cent. This demands use of a sufficient quantity of the salt that the amount of blood taken will result in a dilution which does not fall below this mark. It is best to make up citrate solutions in freshly prepared glass-distilled water immediately before using, since there is a possibility that untoward reactions may occur from long standing even though the solutions have been sterilized.

A. Citration[206]. A one liter Florence flask, A (Fig. 1), containing 35 c.c. of 8 per cent. sodium citrate is stoppered with gauze and autoclaved for fifteen minutes under 15 pounds of pressure. This does not alter the reaction of the citrate or its ability to prevent coagulation. A rubber stopper, B, carrying two glass tubes is boiled together with a No. 19 injection needle and the rubber tubes, E and F. Tube E delivers blood to the flask and should not be more than 5 inches long since it is desirable to eliminate as much contact of blood with rubber as is possible. Tube F, allows the operator to exert suction. This apparatus avoids stirring the blood and contact with the air. It delivers the blood through the long glass tube directly into the citrate without dripping slowly down the sides of the flask, and the suction very markedly facilitates collection. Thirty-five c.c. of 8 per cent. sodium citrate should keep fluid 1,400 c.c. of blood. It gives the patient 2.8 gms. of citrate, a dose far below the dangerous limit. Such citration insures a strength great enough to restrain coagulation in the 600 or 800 c.c. of blood ordinarily withdrawn, and after repeated observations we are assured it causes no hemolysis within three hours' time. Citration has also been accomplished by using 2.5 per cent. sodium citrate in freshly distilled water in the proportion of 10 c.c. to 90 c.c. of blood, and a 2 per cent. solution in

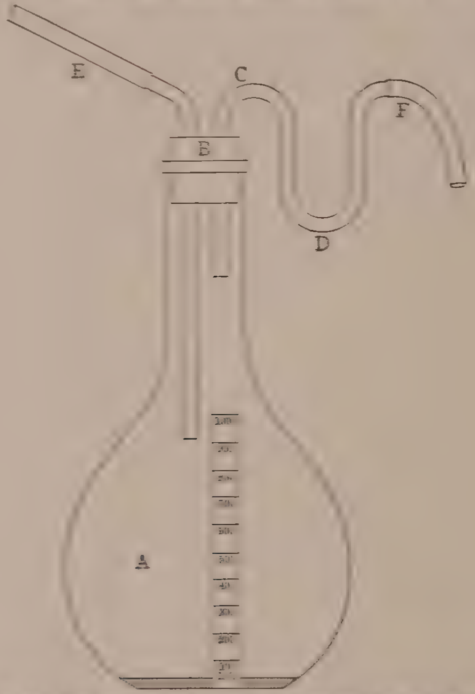

FIG. 1.—Collecting flask containing sodium citrate solution.

the same proportion. These alterations do not change the frequency of reaction occurrence.

B. Injection. The apparatus in Fig. 2 is used. It is convenient to clean and carry about and brings the blood in contact with a minimum amount of rubber. A fine injection needle, No. 21, is thrust into the recipient's vein and with blood flowing freely connection can be made and the donor's blood forced in. Robertson[illegible] has recently pictured a combination removal and injection apparatus very convenient for emergency work. As routine, however, we believe the blood should be filtered before the final injection. This is readily accomplished by filtration from the collecting flask into the injecting flask, an old, fine mesh, sterile towel being used as a filter.

All glassware, both for collection and injection of blood, is cleansed in hot tap water and rinsed with fresh glass-distilled water before being tied up for sterilization. Needles and short delivery tubes are boiled in tap water and shaken dry before use. For all solutions coming in contact with blood, glass-distilled water is to be used and solutions should be made from water distilled and sterilized on the day of use, while all salt solution used for direct injection is to be made from water distilled and sterilized on the day of use.

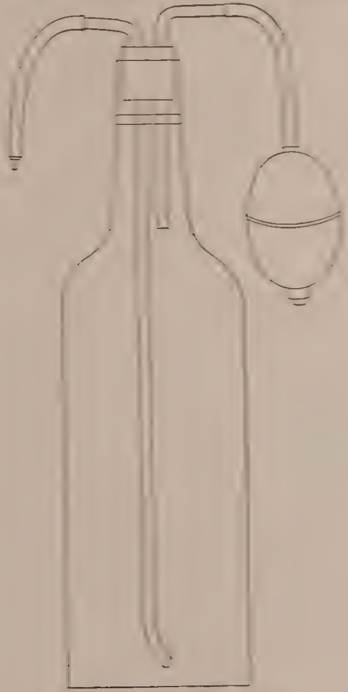

FIG. 2.—Injecting flask.

Technic of Transfusion with Blood to which no Substance is Added.—Lindeman's[211] method is admirable for giving whole blood, altered in the least possible manner, but it requires a good deal of assistance. Briefly stated, it is as follows:

The apparatus consists of two sets of cannulae, two tourniquet and twelve 20 c.c. record syringes. There are three cannulae to each set, telescoping within each other. The innermost is a hollow needle, two and six-sixteenths inches long, 20 gauge, with one end ground to a fine point and short bevel

This needle or cannula number one is fitted into cannula number two, which is slightly shorter than the needle. Cannula number three is slightly shorter than number two and is two inches long and 14 gauge. The first two cannulae are fitted inside the third. The proximal ends of cannulae one and two are capped with a stationery thumb screw, while the proximal end of number three is made to fit a record syringe. After the tourniquet is placed on the donor's arm and the skin sterilized, the cannulae are gradually inserted by skin puncture into the vein in the following manner. After the first joint between the distal ends of cannulae one and two has entered the vein, cannula one is withdrawn about one-half inch. This prevents the vessel wall from being injured by the needle of cannula one after the vein has been entered. The cannulae are now forced in until the second joint, the one between cannulae two and three, has entered the vein, and then cannula two is withdrawn half an inch. Cannula three is now gently pushed into the vein a desirable distance usually about three-quarters of an inch, and cannulae one and two are entirely withdrawn. When the blood first appears, syringe of warm saline solution is immediately attached, and a slow flow of saline is maintained through the cannula. Escape of blood is thus prevented. A cannula is then inserted in the vein of the donor and syringe with salt solution attached. An empty syringe is substituted for the one containing salt solution connected with the donor's vein, and blood is withdrawn as rapidly as possible. When full, the assistant passes it to the operator on the recipient, who evacuates its contents into the vein of the patient. One syringeful of blood is followed by another in rapid succession until the desired quantity has been given. A little saline from time to time may be injected through the cannula of the recipient to keep a free flow of blood. The syringe should be cleansed in sterile water before using a second time. Air must be avoided. Speed and dexterity are requisite. Simple needles and larger syringes may be used. The same vein can be repeatedly used.

Another method for giving whole blood involves the use of paraffined cylinders, particularly described by Kimpton and Brown[212]. Various modifications of this technic have been devised, that of Vincent's[213] being briefly as follows:

The apparatus that holds the blood is a glass cylinder affair with a capacity of either 250 or 300 c.c. This is coated with paraffin. The upper end of the cylinder is closed firmly with a cork. Three centimeters below this is a side opening, where connection is made with a bulb syringe used to express the contents of the tube. The lower end of the cylinder terminates in a glass tip, through which the blood enters and leaves the tube.

A blood pressure apparatus is put on the donor's arm as a tourniquet and kept at a pressure of about the diastolic pressure. By means of a short rubber connection, a large bore needle coated with paraffin, which is inserted in the donor's arm vein, is connected with the cylinder. Blood flows into the cylinder, the donor opening and shutting his hand to aid the flow. When filled, the tube is disconnected from the donor's vein and during transfer to the patient is kept in a horizontal position, with the finger over the hole in the upper end to prevent escape of blood.

The patient's arm having been prepared previously to receive the blood, it is forced by the bulb syringe out of the cylinder into the patient. The patient's vein frequently has to be exposed by skin incision and an incision made in it so that the glass tip of the cylinder is inserted directly into the vein, which latter must be tied off. When the character of the veins permits, a large bore needle can be inserted by skin puncture into the patient's vein without incision. Needle puncture for the donor is usually always possible, but when the veins are small a skin incision may have to be made.

While the first tube is being emptied, a second tube may be filled, or one may remove the needle in the donor's vein and obtain a second tube at one's leisure. The preparation of the tubes and needles requires some practice but is not difficult. They may be kept when once prepared indefinitely and are then always ready for immediate use.

(*d*) *The Amount of Blood to Give.*—An average amount of blood to be given an adult is 450 to 700 cubic centimeters. This amount usually can be readily taken from a donor without causing discomfort. The general opinion is that for anemia massive (900 to 1,200 cubic centimeters) transfusions are not so desirable as smaller ones repeated, if necessary, several times. This may well be because the larger amounts hinder regeneration of the patient's blood similarly as in experimental plethora, where a decreased blood formation occurs as shown by Robertson[109] and as observed in patients by ourselves. In some cases of anemia, it seems that regeneration of blood occurs better when greater anemia develops, suggesting that a forcible enough stimulus is produced to the marrow to permit regeneration well above a level at which formerly the patient could not go beyond. Consideration has to be given to such observations when transfusion and the amount of blood to be given is advised.

When transfusion is done particularly because the individual is suffering considerably from a lack of enough hemoglobin to transport oxygen, larger amounts (800 to 1,200 c.c.) of blood are to be given from one or more donors. However, in anemia from acute blood loss one must remember that the important thing usually is to restore volume, and that frequently without transfusion there is enough oxygen-carrying material to sustain life very comfortably. Fluid substances, as gum acacia, may serve in many such cases alone or combined with some blood, thus saving the need of using large amounts of blood from a donor. Large doses should not be given following hemorrhage unless the bleeding is controlled locally, except in instances where the hemorrhage can be dependent upon blood defect such as hemophilia and then large amounts are often desirable.

In giving large amounts of blood it must be remembered that serious symptoms may be produced from giving an excess of any fluid intravenously. As recently commented on by Unger[214], the first evidence the patient gives of hypertransfusion is a series of short sharp coughs. If transfusion is continued the cough will be repeated. Transfusion should not proceed for more than 100 to 200 c.c. beyond the point at which the patient coughs, for the patient may develop pulmonary edema, etc. Other symptoms of hypertransfusion are precordial pain, backache and pain in the legs.

The question of the amount of blood to give and when to repeat it deserves considerably further study, and there are divergent views on these matters, particularly regarding when to repeat transfusion. It is in pernicious anemia that this question particularly arises and it will be referred to later under that heading.

(*e*) *Effects of Transfusion.*—The beneficial effects of transfusion are both immediate, in the sense of hours and days, and remote. By remote we mean persistence of the more immediate beneficial effects, as well as changes caused in the patient, after the actual transfused cells have died. Transfused red cells may live forty days, as Ashby[215] has recently shown, their rate of death being progressive and their length of life depending on the degree of hemolytic activity present in the patient. The white cells live a shorter time, and the platelets but a few days. As the remote effects deal with the ultimate condition of the patient, these will be discussed along with the use and value of transfusion in different anemic conditions.

The immediate effects of transfusion are dependent upon the actual presence of the transfused blood, as well as upon the effect it exerts on the patient's tissues. These effects are as follows:

1. An increase in blood volume with diminution in the rate of blood flow takes place.

2. An apparent redistribution of the blood of a probably mechanical nature follows transfusion. (The donor's cells will be seen in the blood, and should one attempt to diagnose a case following this procedure by blood studies, the presence of donor's cells must be recalled so as to allow no confusion with the patient's own blood picture.)

3. Changes in the red count and hemoglobin percentage occur dependent upon 1 and 2; but such changes vary considerably. Huck[216] has recently discussed these changes. Usually an immediate rise in hemoglobin occurs (some 15 per cent.) reaching a maximum in 24 hours, and the red count rises in a few hours 500,000, often much more, so that it is out of proportion to the amount of blood put in. Following the rise, a fall frequently occurs, so that the count becomes what it was before transfusion, but with the

hemoglobin often higher. Later a rise may occur, and with a favorable course a persistent rise, dependent upon 5 (given below), ensues.

4. Changes, particularly of the white cells but also of the platelets, will occur in twenty-four hours, dependent upon 1 and 2. The most usual change in the white cells and platelets will be a transient absolute increase of the polynuclears, and sometimes of the platelets, whether a transfusion reaction occurs or not. This may be due to a redistribution of the blood with or without a direct response from the marrow, and when present and marked is to be looked upon as a favorable sign, though it does not always indicate that more than transient improvement will occur. However, when the reverse occurs, it is to be looked upon as an unfavorable sign, but in turn does not always indicate further downfall.

5. Besides such mechanical alterations of the blood, and transient evidence of increased marrow activity, definite changes from improved marrow activity, caused directly or indirectly by the new blood, may be seen. The evidence of this may occur immediately following purely mechanical changes, or not definitely for some days or more, more usually the latter slower change. Vogel and McCurdy[217] among others have demonstrated this, and Minot and Lee[61] have discussed it further. In favorable cases, as those types of pernicious anemia with decreased marrow elements in the peripheral blood, evidence of increased marrow activity is first seen in the absolute numbers of the bone marrow white cells remaining at a higher level than before, and secondly, by persistence of increased numbers of platelets. Increases of young red cells begin to appear rather later and remain transiently increased, while the red count of the patient's own cells begins to rise and continues to do so. The regeneration may proceed more gradually and without increase of the young red cells. There may occur a rapid increased activity of the marrow with sharp rises of the bone marrow white cells, platelets and young red cells, which will later fall, but the elements will not reach their previous low level unless this reaction involving all three elements results in no permanent improvement, which is most unusual. There might, of course, occur a marked pouring out of very immature marrow elements which, as previously commented on, is to be looked upon as undesirable. In unfavorable types of anemia as aplastic anemia no evidence of real increased marrow activity will result from transfusion. When the marrow is regenerating blood as rapidly as possible, as following hemorrhage, the demand on the marrow following transfusion, with the increase of hemoglobin, becomes not so great as before and the number of reticulated cells, white cells and platelets will fall.

The blood picture following transfusion will thus vary in different forms of anemia, the effect on the blood forming tissues being to make them act as near normally as they can; for example, doing so by letting orderly regeneration at a desirable rate continue following hemorrhage or by allowing regeneration to increase, as in instances of pernicious anemia.

6. Diminution of the pulse rate and respiratory activity with increase of blood pressure follows transfusion.

7. When there is fever before transfusion, a drop in the temperature commonly occurs during the days that follow transfusion.

8. Diminution of basal metabolism if elevated, as shown by Tompkins, Brittingham and Drinker[218], results from transfusion. The response of the metabolism lags behind the other factors mentioned above, except often those referred to under 5, by an interval of several days.

9. As a result of the above effects, alleviation of symptoms, an improvement in the sense of well-being, diminution of headaches, restlessness, etc., as well as improvement in appetite, etc., ensue at least temporarily. The degree of such symptomatic improvement varies of course with the state of the patient and the cause of the anemia. Following traumatic hemorrhage the immediate results as well as the permanent may be miraculous, while in the myelophthisic anemia due to acute lymphatic leukemia some comfort to the patient physically as well as mentally may occur, but only for a few days. All variations may occur between these extremes.

Transfusion in the Different Anemias

(*a*) *In Anemia Due to Acute Blood Loss.*—The subject of treatment of hemorrhage per se is intimately bound up with that of the treatment of the anemia that ensues, but we shall confine our remarks particularly to the latter. The use of transfusion in instances of acute blood loss has been particularly well described by O. H. Robertson and Bock[219]. Bernheim[182] and Peterson[220] are among many others who have discussed this subject. It is frequently a life-saving procedure.

All individuals with acute hemorrhage do not demand a transfusion as they have not suffered serious enough reduction of their blood elements or blood volume to require it, and the stimulus from acute blood loss is as powerful a one for regeneration of blood as we have. One should be guided by the general condition of the patient as to whether to give a transfusion or not. When in doubt, it is wiser to decide in the affirmative rather than in the negative. The source from which the hemorrhage comes must be taken into consideration.

It is from diminished blood volume that cases of hemorrhage particularly suffer, and forced fluids by mouth and rectum quickly given, provided the source of the hemorrhage does not contraindicate it, probably will frequently save the need of some transfusions. The degree of alteration of the blood volume does not depend wholly on the amount of blood loss, so that it may become markedly diminished, the individuals appearing seriously sick, in some cases with relatively little blood loss. This would appear to be particularly true in instances where some grade of anemia was present before the hemorrhage, and in those individuals who always have a low blood pressure and are asthenic. The blood volume may not be even indicated by the percentage of hemoglobin concentration in the remaining plasma. Special tests, as that of Keith, Rowntree and Geraghty[221], as well as newer ones now being studied, will tell the blood volume rather accurately. However, when the total percentage of hemoglobin is reduced to 25 per cent., transfusion is needful, not only to give more oxygen-carrying cells, but also because it enables the patient to increase his volume. Robertson and Bock[219] have pointed out that the hemoglobin percentage must be above a certain point if rapid restoration of blood volume is to be brought about by the organism's own activity. If the hemoglobin is over 25 per cent., volume increase is the chief need, and then gum acacia solutions may be used alone but even here blood is preferable though mixtures may be serviceable.

Following the initial transfusion, it is seldom necessary to give another, unless hemorrhage recurs or the anemia improves abnormally slowly. It is, however, possible that several transfusions might hasten convalescence.

(*b*) *Transfusion in Anemia Due to Repeated Blood Loss.*—Most satisfactory results are to be obtained in such cases which regenerate their blood more slowly and less well than the acute cases. Even so, they are often not considered quite sick enough to transfuse after the cause of the hemorrhage has been removed, or even when the hemorrhage is still recurring. Transfusion in such cases may improve the tissues so that local ulceration can heal and it will improve the patient in general so as to give him a decent chance to get better by allowing him to eat more and his organs to function more normally. Transfusion should be done in all cases of this type with a marked anemia. In such chronic cases where the red count is in the vicinity of 2,500,000 three transfusions of 600 cubic centimeters some ten days apart will often get the patient back to normal three to five times as fast as if left to himself, while without transfusion such cases may remain in a chronic state for years or die of intercurrent disease due to lowered resistance which might have been prevented by transfusion. Frequently a single transfusion alone will be extremely serviceable, and it is to be recommended in many cases with the lesser grades of this type of chronic anemia, not only as a measure to put the patient in a suitable state for operation on the local cause, but as a measure to hasten convalescence and give the patient a chance to make a satisfactory return to health.

(*c*) *Transfusion in Anemia Particularly Dependent upon Defective Blood Formation.*—Transfusion in these cases depends on the severity of the anemia and its cause. When the cause is incurable, as a malignant growth, transfusion should not be advised but may be urged by the patient or his family.

Single transfusions to put individuals with simple chronic anemia into a suitable condition for operation are wise. When the anemia is curable or it is felt that the cause may be lessened by transfusion, blood may be given similarly as in chronic anemia from hemorrhage.

When an anemia is dependent upon a condition like benzol poisoning, which severely injures the marrow and may cause complete aplasia, transfusions should be used repeatedly and the case not given up until very many, more than ten, transfusions have been given. This is because, having removed the cause, by keeping the patient living by the aid of the donor's blood, which also checks the hemorrhage of the symptomatic purpura hemorrhagica, we may tide the patient over a period of time until his marrow regenerates enough to functionate sufficiently to form suitable amounts of blood. The time to repeat transfusions in such a case is with the onset of further distinct evidence of bleeding or when the patient ceases to gain definitely in a two-week period. In some cases, permanent recovery does not ensue because the damage to the marrow has gone so far that it cannot be repaired. Good results from repeated transfusion in benzol poisoned cases have been reported by McClure[222], and we have seen the same.

(*d*) *Transfusion in Chlorosis.*—Transfusion in chlorosis is not indicated except possibly when the anemia has been persistent and of a marked degree.

(*e*) *Transfusion in Myelophthisic Anemia.*—Transfusion alleviates but temporarily, as the cause of the anemia cannot be removed. Thus one cannot feel quite justified in keeping such a patient living for a few days longer by means of a donor's blood, though if bleeding is pronounced, one may wish to transfuse so as to check this disagreeable symptom with the hope that death may ensue and end the patient's sufferings before the bleeding recurs.

(*f*) *Transfusion in Idiopathic Aplastic Anemia.*—In idiopathic aplastic anemia transfusions have so far caused but very temporary benefits. The patients are filled up with foreign blood only to die of the disease about as soon as if they had not received it. To be sure, we never can tell when we may have a case that may respond like the cases of benzol poisoning, and some cases of partial aplasia due to infections may perhaps be able to respond to repeated transfusions. Thus, we cannot say that blood should not be given to cases diagnosed as idiopathic aplastic anemia or secondary aplastic anemia in a similar manner as that advised for benzol cases, but the advantages to be gained, from our experience and that of others, are not at all promising.

(*g*) *Transfusion in Pernicious Anemia.*—Transfusions in pernicious anemia never cure the disease and they do not prolong life to any significant degree. There are many publications touching upon this subject. Those of Ottenberg and Libman[170], Bloomfield[71], Meleney and others[175], Archibald[60] and Minot and Lee[61], cover this subject.

Transfusions may be employed in relapses to relieve symptoms and with the hope of bringing about a remission. Transfusion appears to give more constant remissions and rather better ones than any other form of therapy, except perhaps splenectomy. It is possible, however, to parallel the most marked remission by either of these procedures together or alone with a case that has had no such treatment. The chances of a spontaneous remission occurring when a case is seen in a relapse is in the vicinity of 35 per cent. Transfusion in all types of pernicious anemia taken together, appears to bring about 10 to 20 per cent. more remissions than occur spontaneously. Such remissions are apparently dependent upon something more than simply filling the patient up with blood. In selected cases, the chances of a remission are probably greater. Not only does transfusion increase the chances of a remission but if a definite remission occurs the degree of improvement that the patient experiences following transfusion averages rather definitely better than that resulting from spontaneous improvement. However, the duration of remissions aided by transfusion is in no wise different from the spontaneous remissions.

No case is too sick to receive a transfusion, but if one decides to transfuse, it should preferably be done before the blood volume or red count becomes extremely low, and one should not wait until the patient has been in a state of relapse for many weeks. It would seem desirable by transfusions to keep the patient above the level of marked anemia in view of the evidence that anemia per se causes deterioration of the various organs of the body, and by so doing, one may perhaps induce remissions at a later date that cannot be induced at the time. It is probably wise not to transfuse at the time of an acute hemolytic crisis.

The cases that are apt to receive the most benefit from transfusion are the same as those most likely to have spontaneous remissions and run the best course of the disease without transfusions. Patients who have had or may be expected to have definite remissions, receive the most benefit from transfusion, so that a careful study of the blood factors and the clinical state of the patient will often tell what is to be expected from transfusion. Also a study of the basal metabolism appears to tell us what to expect from transfusion, for Tompkins, Brittingham and Drinker[218] have shown that when the metabolism is as much as minus 10, it indicates that comfort may occur from transfusion, but that there is little probability that it or other transfusions will do more. When the metabolism is plus 10 or more, transfusion is well worth while, for if the metabolism does not fall too low following the procedure, definite benefit is to be anticipated and further transfusions are indicated. Probably future metabolism and blood studies of various types will tell us more about when it is worth while to push transfusions and when they are likely to be of but temporary value. It is certain.

however, that transfusions for pernicious anemia are not to be used promiscuously and every time a case is seen in a relapse, because they cannot by any means always do good except perhaps in a very temporary manner. For example, in an elderly case that has had a prolonged downward course with slight remissions for a period of two years one cannot expect, though it may occur, more than slight temporary benefit from transfusion, and in such an instance it cannot be urged or perhaps really advised. On the contrary, with a young individual seen at the time of his first marked relapse, transfusion repeated several times is to be urged. Thus one must weigh the chances of remission, the state of the patient both clinically and as determined by laboratory methods, as well as the wishes of the patient and his family, when deciding to urge transfusion in these cases. Just because a case seems hopelessly sick a transfusion should not necessarily be rejected, for it is not to be forgotten that a case may be in such a state and yet show remarkable gain following the procedure. In such instances, transfusion may for the time being be life-saving, though even here it must be admitted that spontaneous, marked remissions may occur following a period of time when the patient appeared moribund.

One transfusion is often to be advised in any relapse, and it can do no harm, but according to the condition of the patient as alluded to, may be urged or given in the spirit of simply trying to do something for the patient and his family. When the result of one transfusion is followed by evidence of definite improvement which appears to depend upon more than purely the presence of foreign blood, a second one is often to be advised seven to fourteen days later, sooner, if serious blood volume reduction or low counts are present. If rapid improvement is occurring, a second one may be postponed, while with improvement more may be given to hasten the remission and improve its degree. In relapses where the first transfusion gives no evidence of improvement, a second and third may be tried, but only infrequently will they yield significantly better results. Several transfusions, however, are to be tried when one considers the patient a type of case that should improve. It is a fact that two or three transfusions at one time may be followed by no noteworthy remission, while at another they may give good results, or spontaneously the patient may at a later time have a good remission when none followed the transfusions. Such a state of affairs is unusual. Anders[223], in reviewing the literature recently, has found that, of 362 cases receiving transfusions at the time of a relapse, an average of 2.4 transfusions were given each patient and that relatively small (500 c.c.) transfusions were usually given. It seems that the best gains, and thus better remissions, have been reported when repeated transfusions of relatively small amounts but giving a total large amount of blood were used. The benefit in some such instances is probably wholly dependent upon the life of the transfused blood, though in others it appears to permit a desirable remission sooner than when lesser total amounts of blood are used. If plenty of donors are available and one feels that the patient wishes to be simply filled up with blood and live as comfortably as he can on foreign blood, transfusion may be done more often than when one aims to use transfusion to initiate a remission sustained by the patient's own blood, but initiated at an increased rate with a better degree of improvement than usually occurs spontaneously.

From this discussion some may derive an unfavorable impression of transfusion in pernicious anemia. However, it is the one procedure that can be successfully employed to relieve symptoms in these patients, except those definitely referable to changes in the central nervous system. It is also to be noted that frequently following relief from one transfusion, the patient requests another, so that often transfusions may have to be given to keep the patient comfortable, though as a chronic invalid. Though such may be the case in some instances, we must realize that transfusion is a very valuable procedure in others. Many cases treated in such a manner are more likely to show constant temporary improvement and be more comfortable while they live than without such treatment. The state of the patient, and his wishes, as well as the availability of donors, should determine when to transfuse and whether to repeat the procedure.

(*h*) *Transfusion in other Anemias than Pernicious Anemia in which the Hemolytic Factors play an Important Role.*—In these conditions transfusion is to be done when the anemia is marked and acute or when chronic and moderate. Repetition of transfusion is seldom desirable in this group of cases if the cause cannot be removed, or if the transfusion does not act to minimize the cause, as it may do in some cases that are due to chronic sepsis. When the cause is removed, the use of repeated transfusions is valuable and should be continued so long as the patient ceases to improve or when he does so abnormally slowly. When marked methemoglobin formation is present, as in some acute cases due to poisons, the giving of normal oxygen carrying cells may be life-saving.

In acute hemolytic anemia due to overwhelming sepsis, transfusions will probably be useless, but they may be advantageous in cases of chronic hemolytic anemia associated with sepsis, especially when also associated with hemorrhage as occurs with puerperal anemia proper. The use of transfusion in the various forms of anemia that may occur with pregnancy has been well stated by Guillaume[224].

Transfusion does not check hemolysis, though hemolysis may decrease with improvement of the patient, so that when cases of chronic hemolytic jaundice and idiopathic cases of chronic hemolytic anemia, of preferably at least a year's duration, are sick enough to demand transfusion, splenectomy rather than transfusion is the treatment to be advised. Transfusion before splenectomy may be necessary to put the patient into a suitable condition for the operation, and blood may be given following this operation to shorten the patient's convalescence.

(4) *Splenectomy.*—Splenectomy alters favorably red cell destruction and blood formation, the histological blood picture following splenectomy varying with the diseased condition of the patient. This procedure and its results are particularly discussed under the section on Diseases of the Spleen.

Of the anemic conditions referred to in this section splenectomy is particularly indicated in the various forms of chronic hemolytic jaundice provided the patient is ill enough to be distinctly handicapped. The results in these conditions are often very beneficial and sometimes apparently curative[225]. As chronic hemolytic jaundice is fully discussed under Diseases of the Spleen, Vol. IV, by Sailer, it will not be referred to here further.

In the ill-defined idiopathic cases of chronic hemolytic anemia with large spleens and in some instances where the cause of such an anemia is recognized, yet where treatment has not stopped the hemolytic process, splenectomy may be undertaken with the expectation of definite benefit to the patient.

Besides the conditions discussed under diseases of the spleen and those which have just been mentioned pernicious anemia is the only other condition in which splenectomy may at times be done. In pernicious anemia the results have been disappointing since Eppinger[44], von Decastello[226], and Klemperer and Hirschfield[227] first reported on this procedure. A considerable number of cases have now been reported and the results are in no way at all as beneficial or satisfactory as in chronic hemolytic jaundice and in Banti's disease. Krumbhaar[228] has given an excellent summary of the results in pernicious anemia. Giffin's[229] and Lee, Minot and Vincent's[230, 61, 103] papers, among others, discuss the subject.

In unselected cases of pernicious anemia, splenectomy is followed more consistently and uniformly by a remission of a good degree than following any other procedure. Some 70 per cent. of essentially unselected cases have shown some definite improvement. Even so, the duration of the remissions and the progress of the disease is essentially the same as with other methods of treatment and the procedure does not significantly prolong life. The most recent report is by Hirschfield[231], who found that the thirteen cases he followed all died within four years after the operation. Thus this serious operation is only palliative and is under no circumstances to be urged, but in selected cases may be advised. Vastly more often it should not even be considered, for though the response to the procedure may be temporarily very good, it is altogether too much of an undertaking for the amount of possible good to be gained. This is not only because of the purely temporary gain, but also because of the risk of mortality at operation and the complications that may follow, especially thrombosis associated with the high tide of platelets occurring after the procedure.

Splenectomy may be advised in those rather rare cases of pernicious anemia with large spleens and considerable constant hemolysis without a marked degree of anemia or spinal cord symptoms that approach in character chronic acquired hemolytic jaundice. This is because it has been shown that such cases do better than others and live more comfortably and perhaps longer with their spleens out than with them in. In this type of case the exact diagnosis is often difficult. The more closely such cases are related to acquired hemolytic jaundice the better the result we may anticipate from splenectomy.

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CHAPTER XVII

LEUKEMIA

By THOMAS ORDWAY and L. WHITTINGTON GORHAM

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GENERAL CONSIDERATIONS

The definition of the condition known as leukemia, as it is generally understood at the present time, may be modified to include numerous atypical cases and related conditions. Such conditions are referred to by Hirschfeld[1], Barker[2] and others as the subleukemic and aleukemic myeloses and lymphoses many of which have a certain resemblance to pernicious anemia. Marked numerical and morphological variations in the blood may occur not only in different individuals, but in the same individual at different times during the course of the disease. The conception of the term leukemia would thus be broadened to include not only unusual cases but conditions frequently classified as tumors, such as chloroma and various lymphomata; it is difficult in certain instances also to separate some of these conditions from the granulomata, notably so-called Hodgkin's disease. All of these tumor-like conditions may at times show changes suggesting a leukemia or an aleukemic character in the blood.

From the above we may infer that there is a great variety of conditions characterized by all degrees of changes in the blood and blood forming organs, the bone marrow, lymphatic nodes, the spleen, and in certain instances the tissues generally. Some of these conditions have a fairly definite, even characteristic, clinical picture. Others are very atypical and variable. By a careful study of the latter cases we may hope to supply many gaps in our knowledge of leukemia and related conditions. This conception of leukemia in relation to other pathological processes, notably the infections and the tumors, is somewhat analogous to the development of our knowledge of various forms of ether vibrations in the so-called energy or frequency spectrum[3]. At first we recognized only the visible light spectrum. Later the infra-red and ultra-violet became manifest by their heat and chemical properties respectively. More recently we find the long Hertz waves, far to the left of the infra-red, made use of in wireless telegraphy. To the extreme right of the ultra-violet are the so-called Lyman rays and further out to the right the Roentgen rays and still further the Gamma rays of radium. Even now this frequency spectrum is not complete, but knowledge gradually accumulating has permitted us to conceive the whole. So in leukemic conditions we have at present knowledge of only separate fragments. Additional research and record may show the true relationship of one part to another and to the general plan of pathologic conditions, notably the infections and the tumors.

Leukemia is a striking example of the fact that when the specific cause of a disease is still undiscovered, it may be impossible clearly to define its limits, and to arrange our accumulation of isolated observations regarding the disease in orderly sequence with a proper conception of cause and effect. It was not until the painstaking pathological studies of Louis and the isolation of the bacillus by Eberth, that typhoid fever emerged completely from the great group of fevers as a sharply outlined clinical picture. Lacking the coordinating force of a well established etiology a vast literature has grown up dealing with the subject of leukemia. It represents the efforts of authors to record the characteristics of the disease by all the methods of study known at the present. The literature also contains endless hypotheses and speculations as to the cause of leukemia, and as to its relation to other diseases, particularly the infections and the tumors.

This article will deal more particularly with the recent work in leukemia, and no attempt will be made to duplicate the comprehensive surveys of previous authors—Muir[4], Cabot[5], Barker[2], Naegeli[6], Herz[7], Pappenheim[8], and others. The presentation, therefore, of the subject of leukemia resolves itself into the recording of the facts regarding the disease which various methods of study have yielded, and into a discussion of the possible etiology and relationships. Classification of some sort with the knowledge at hand must be attempted, yet it is to be realized that this is only tentative so long as the specific cause remains unknown.

The general conception of leukemia, or leukocythemia, is that it is a disease of the blood forming tissues which produce leukocytes, manifesting itself by a marked hyperplasia of these tissues. When fully developed in its classical form it is characterized clinically by a remarkable increase in the number of white blood cells in the blood, and by varying grades of splenic and glandular enlargement. The white corpuscles of leukemic blood vary from the normal leukocyte in many instances and are considered pathological unripe cells which have gained access to the blood before reaching maturity. It is not the increased number of white blood cells, but their immaturity which distinguishes leukemia from leukocytosis. Increased knowledge has forced us to extend the bounds of this definition of the old classical leukemia, for there are cases in which the blood picture is characteristic of leukemia and yet autopsy shows no evidence of leukemia.

These cases may be considered as instances of an abnormal response of the bone marrow to infection. On the other hand, cases are seen in which the blood picture is subleukemic or even normal, and yet autopsy reveals leukemic changes in the tissues.

It is evident, therefore, that the essential point in the diagnosis of leukemia is the hyperplasia of the leukocyte producing tissues, and not the presence of an excessively high white count, nor the discovery of a certain percentage of abnormal white cells, which differentiate it from ordinary leukocytosis. The distribution of this cellular hyperplasia may vary in the individual case but it has the same general characteristics in all.

Our present point of view, therefore, considers leukemia as consisting of several states rather than as a single disease picture, and so has been termed "leukemic states." All of these states, however, are consistent in showing histological evidence of leukemic hyperplasia, although clinically and hematologically there may be extreme variations from the generally accepted picture of hyperleukocytosis, enlarged spleen and lymphatic glands. Such a concept would include, therefore, the leukemic and subleukemic and aleukemic myeloses and lymphoses.

Our first knowledge of leukemia dates from 1845, when Virchow[9], and independently of him Hughes Bennett[10], described the peculiar white appearance of the blood at autopsy, the massive enlargement of the spleen, and the presence of exceedingly large numbers of leukocytes in the blood. The former called the disease "leukemia," and the latter "leucocythemia." Both failed to distinguish any qualitative change in the white blood cells from those of sepsis. Virchow[11] later drew attention to the type of leukemia in which the lymph glands were principally affected, while the spleen was relatively unaffected. He then made a distinction between the "splenic" and "lymphatic" leukemia. A notable contribution to our knowledge was that of Neumann[12], who discovered changes in the bone marrow in cases of leukemia and proposed a third type, "myelogenous leukemia."

Because of the varying degrees in which glands, spleen and the bone marrow were involved, often in contradictory manner in cases apparently alike clinically, there was much difficulty in properly classifying the types of leukemia. An arbitrary figure of 50,000 white blood cells was taken as the dividing line between leukemia and leukocytosis. Our present conception of the disease sweeps away all such arbitrary classifications or divisions made on clinical lines or by numerical differences in blood counts and lays all the emphasis on the type of cell encountered. This is due to Ehrlich[13], whose differential staining of leukocytes (granular or non-granular) enabled him to classify the varieties of the disease according to the type of cell instead of on the clinical basis which depended upon the organ principally affected. This is the corner stone of the pathology of leukemia.

Ehrlich enabled us to distinguish two great groups of leukemia, (a) myelogenous leukemia with hyperplasia of the white cells of the bone marrow (granulocytes), and (b) lymphatic leukemia with increase of the lymphocyte series of non-granular cells. The spleen was thus omitted as a factor and hence the matter of classification was simplified. The "splenic" form was found to show bone marrow changes with hyperplasia of the myeloid elements and was, therefore, termed "myelogenous" or "spleno-myelogenous" type of the disease. Further it was shown that the lymphatic type might eventually also show a characteristic lymphoid proliferation in the marrow. Thereafter Ehrlich made the division regardless of the size of the organs affected but solely on the basis of whether the hyperplasia throughout the blood and various organs was composed of myeloid cells (granulocytes) or of lymphocytes (non-granular cells). He regarded the hyperplasia as metastatic, starting from bone marrow or lymph glands. This is the basis upon which is founded the dualistic theory of the origin of blood cells.

In succeeding years a large number of cases of leukemia were reported which could not be clearly classified as purely myelogenous or lymphatic because granular and non-granular cells appeared together in the blood (mixed leukemia), or a known myelogenous leukemia just before death was found to show a large percentage of non-granular cells (changes from myelogenous to lymphatic leukemia). These cases were classed as "atypical leukemia." One group of authors represented by Pappenheim seeks to explain these cases on the theory that both lymphoid and myeloid cells come from a single undifferentiated mother cell[14].

Since 1900 the conception of Naegeli[6] has gained in credence. His view, amply confirmed, is that the pre-stages of the myelocyte (the myeloblasts) although closely resembling lymphocytes, are actually different morphologically and do not originate from lymphoid tissue but from myeloid tissue. These are the non-granular cells which sometimes appear in myelogenous leukemia causing confusion and the diagnosis of mixed leukemia. They are not lymphocytes but are members of the myeloid series of cells. The use of the oxydase test, especially as modified by Graham[15], has given support to this theory. Thus the dual origin of the blood cells is favored by the majority of hematologists. In support of this view is much recent hematological, biological, chemical and experimental evidence although the question of the origin of the blood cells is still an open one (see Drinker, Vol. II, Chap. XV).

Occurrence of Leukemia

The condition known as leukemia has wide distribution in the animal kingdom. It is of frequent occurrence in fowl in the spontaneous form and it may also be induced experimentally[16, 17, 18].

In 1909 Tyzzer and Ordway[19] reported a series of tumors in the common fowl among which was a case of lymphoma associated with lymphatic leukemia and five cases of lymphoma without invasion of the blood stream. The pseudo or aleukemic variety in fowl has been described also by Nihonmatsu[20]. As early as 1858 Leisering[21] described leukemia in animals stating that it is more frequent in dogs than in other house animals. Up to 1889 only five cases of leukemia in swine had been described. Aubertin and Morel[22] have shown that lymphatic leukemia is well known in the dog and in the pig but is considered rare in cattle although lymphadenie, the aleukemic form, is reported by veterinarians in the calf, ox and cow. Many of the cases have not been sufficiently studied to draw accurate conclusions regarding their true nature. These authors believe that lymphatic leukemia in cattle is an established fact and suggest that it would be interesting to study the connection and transition between lymphadenie and lymphatic leukemia.

Wells[23] states that in studying mice in the course of tumor work a lymphatic condition indistinguishable from leukemia and pseudoleukemia in man has been repeatedly observed. Nothing exactly like the lymphogranulomatoses or Hodgkin's disease has been found although there are many obscure forms of lymphatic or splenic hyperplasia. Slye[23] has found that true leukemia and pseudoleukemia in mice occur only in strains that have tumors and in heredity studies these diseases behave exactly as the

All Ages to Age of	Acute Leukemia		Chronic Lymphatic Leukemia		Chronic Myelogenous Leukemia	
	M.	F.	M.	F.	M.	F.
5	60	40	..	..	..	..
10	65	35	..	..	..	..
15	69	31	75	25	60	40
20	72	28	80	20	61	39
25	71	29	83	17	55	45
30	71	29	81	19	52	48
35	70	30	76	24	52	48
40	69	31	86	14	52	48
45	68	32	75	25	53	47
50	68	32	77	23	55	45
55	67	33	75	25	54	46
60	67	33	77	23	56	44
65	..	..	73	27	56	44
70	..	..	74	26	56	44
75	..	..	74	26	56	44
80	..	..	75	25	56	44
85	..	..	..	..	56	44

Fig. 1.—Table showing proportion of sexes at various age periods. Taken from article by Ward, *British Journal of Children's Diseases*, 1917, XIV, 10.

true tumors. They have not, however, been successfully inoculated into normal mice in spite of many attempts. These observations lend support to the view of those pathologists who maintain that leukemia and pseudoleukemia are tumors of the myeloblastic and lymphoblastic tissues.

Age and Sex Incidence

In human beings leukemia occurs at practically all age periods. There is, however, a marked preference for the male sex and each of the three forms of leukemia, acute leukemia, chronic myelogenous and chronic lymphatic leukemia, has a definite age of election. This is indicated in the charts and tables presented by Ward[24].

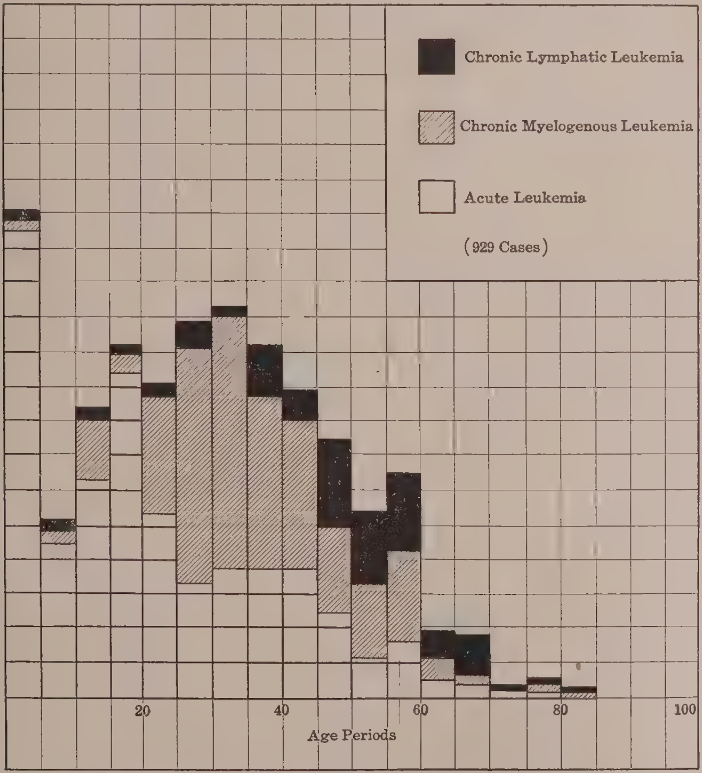


FIG. 2.—Age incidence (in five year periods) of all varieties of leukemia subdivided to show the proportion of each variety at each age. Note especially the sharp fall after 60 and the relatively small number of cases in the second age period—years, 6–10. Taken from article by Ward, *British Journal of Children's Diseases*, 1917, XIV, 10.

Fig. 1 shows the incidence in each five year period of 398 cases of acute leukemia, 84 cases of chronic lymphatic leukemia and 247 cases of chronic myelogenous leukemia. Of the latter the majority of cases are between the years twenty-five and forty-five. Chronic lymphatic leukemia occurs later and shows the majority of cases between the ages of forty-five and sixty. In acute leukemia, on the other hand, there is a decided preference for ages below twenty-five and in this period the maximum incidence is in the first five years falling sharply in the next five but rising to the second maximum between the years of fifteen and twenty.

Fig. 2 shows the incidence by ages in 929 cases of all varieties of leukemia. There is a marked fall after the age of sixty and a relatively small number of cases in the second age period, six to ten years. In the first age period, one to five years, the number of cases is highest and of these acute leukemia makes up almost the entire number. It is doubtful whether all of these cases in this age period are really acute leukemia for at this age the blood response to various abnormal conditions, chiefly infections, is very marked not only in the relative increase in certain types of white cells, notably the lymphocytes, but also in the absolute number of white cells.

The number of cases of leukemia occurring in children is not so small as was previously thought. In the very young the condition is very liable to be overlooked. In acute febrile forms it is easily mistaken for typhoid fever or paratyphoid fever or the ulcerative stomatitis and hemorrhages may cause it to be mistaken for malignant diphtheria, scurvy, purpura, or some severe infection[25]. Adler[26], 1914, has searched the literature since 1845 and found only seventeen reported cases of leukemia in infants. He also emphasizes the frequency with which the diagnosis in infants is mistaken for other conditions.

Myeloid leukemia is rare before the sixth year, but there are several carefully studied cases of myelogenous leukemia in infants. Knox[27] described a case of myelogenous leukemia in an infant nine months old. He believed this the youngest case on record in which the blood picture was characteristic. Pisek[28] also reports a case of acute myelogenous leukemia in an infant fourteen months of age. Cassel[29] in a series of 3,000 autopsies found only two cases of leukemia during the first decade of life. The myelogenous variety of leukemia in young children is believed to be at least five times more rare than the lymphatic form. Pisek[28] states that in a careful search of the literature up to 1916 only nineteen authentic cases of myelogenous leukemia were found in children and only seven of these were less than two years of age.

Although the leukemic condition, as shown in chart, Fig. 2, shows a sharp fall after the age of sixty, occasional cases have been reported in elderly people. Pinelis reports a case of acute leukemia in a man seventy-three years old. We have observed a case of chronic myelogenous leukemia in a woman seventy-five years old.

Heredity

Various authors have suggested a possible hereditary factor in leukemia in man but there is very little evidence in its favor. The familial character has been noted. There is, however, little or no valid evidence that heredity is related to the development of leukemia in the human being. In mice Slye[23] has found that true leukemia and pseudoleukemia occur only in strains that have tumors and in heredity studies these diseases behave exactly as the true tumors.

Pregnancy

Marmol[30] cites a fatal case of acute leukemia in a young woman less than two months after a normal childbirth. There were 91.3 per cent. of mononuclear cells. Ward[24], in his review of the literature, found fifteen cases of leukemia during pregnancy and four in which the disease was recognized soon after parturition. The writers have personally seen two cases associated with pregnancy, one of which was in the latter months of pregnancy and the presence of the greatly enlarged spleen was less evident because of the gravid uterus. In the other case the leukemia was noted a few months after parturition. Although the actual relationship of pregnancy and parturition to the development of leukemia is not proved it seems possible that in certain individuals the extra demand upon their blood forming organs might result in the very abnormal response characterized by the condition of leukemia.

Transmission

In confirmation of the work of previous investigators[16, 18, 31] leukemia of the fowl was successfully transmitted in the same species from a spontaneous case into the fifth generation by Schmeisser[32] by intravenous and intraperitoneal injection of organ emulsion. The transmission of the disease by Schmeisser is of special interest as the strain originated in an animal absolutely unrelated to that of previous investigators. Schmeisser transmitted leukemia of fowls to more than twenty-five animals and all cases, with the exception of one in which there was a spontaneous cure, went on to death. His experiments with the inoculation of leukemic material of human beings into monkeys have been negative.

The occurrence of a typical case of leukemia in the course of the experimental transmission of an acute disease of the fowl known as fowl typhoid[33] suggests a close relationship between these two conditions. In the animals that do not die acutely after the first injection of the fowl typhoid bacillus there is an intermediate stage characterized by changes in the blood picture and along with this myeloid infiltration of the organs may also occur.

This suggests the possibility of producing typical chicken leukemia by properly regulated doses of the bacillus of fowl typhoid. This work is of considerable interest from the point of view that the condition, leukemia, is not a distinct entity but an unusual blood reaction to various agents. In the fowl, however, in comparison with mammals the inflammatory response to stimuli is unusually marked. This tissue and blood response characteristic of the fowl, as shown by the work of Winternitz, Schmeisser, and by Rous in the so-called chicken sarcoma, makes it impossible to apply directly the results of studies in fowl to similar conditions in man.

Sellards and Baetjer[34] report experiments on the attempted transmission of leukemia to monkeys. They believe that the splenomegaly and the blood picture is suggestive though not typical of leukemic changes. As a result of their observations they concluded that an abortive transmission of leukemia had been obtained differing in some respects from the typical picture perhaps on account of the natural resistance of these animals to the disease.

In the interpretation of the work of Sellards and Baetjer, however, Welch believes that much depends on the problem of the mononuclear cells. If these are not myeloblastic in origin one might hesitate to regard the condition as true leukemia.

Varieties and Types of Leukemia

In addition to the usual classification of leukemia into chronic myelogenous, chronic lymphatic and acute leukemia, the latter variety being further subdivided into the myelogenous and lymphatic types by certain observers, it has been suggested by Ward[35] that the leukemias be considered and classified in a manner similar to that which is the usual custom in anemia, that is, that leukemias where no contributing causal factor is discernible be considered as *primary* and all other leukemias as of *secondary* type. In other words he would regard the ordinary leukemias as primary and the symptomatic leukemias as secondary.

Primary leukemia would indicate the response of the blood forming organs to a stimulus of unknown nature. This stimulus is thought to be aroused by excessive destruction of white blood cells and in response to this there is a great and irregular exaggeration of white cell formation. The liver and even parts of the body which are not associated with blood formation in fetal life take part in this process of white cell formation and this fact is one of the surest criteria of the presence of leukemia. Such a hyperplasia suggests a response to the demands of this hypothetical stimulus. Hence it is assumed that we must have primitive cells, hematoblasts or hemoblasts, capable of forming blood cells under the influence of a special and particularly powerful stimulus. The mechanism by which newly formed white cells of the lymphocytic and bone marrow series gain access to the blood stream is little known but from clinical evidence it seems to be a very variable factor even in individual cases. This variation may account for the aleukemic phases in leukemia.

In the so-called *secondary leukemia* the full picture of primary leukemia is rarely met with. In certain infectious diseases there may be a marked lymphemia. Cabot[36] reports four cases in which the blood picture was very similar to a primary lymphemia. These were apparently due to infection and all recovered. One was known to be alive fifteen years later although the lymphocytes were seventy per cent. Cabot also reports two cases of pneumonia, one a year and three months and the other six years of age. Both also had pertussis. In one the white count was 185,000 with sixty-four per cent. of lymphocytes and in the other 94,000 with sixty-six per cent. of lymphocytes. Stevens[37] reports a case of bronchopneumonia in a child one year and ten months old in which the white count was 236,000, lymphocytes sixty-five per cent. Austrian[38] reports a case of bronchopneumonia with mastoiditis in a child four years old. White cells were 192,000, lymphocytes ten to fourteen per cent., total myelocytes per c. mm. 23,000. There were also many unclassified cells. Autopsy showed marked hyperplasia of the marrow with neutrophilic myelocytes predominating. Malpighian bodies in the spleen were gray and greatly enlarged. The parenchyma of the liver was infiltrated with mononuclear cells and occasional myelocytes. The bronchial and mediastinal glands were much enlarged. Hirschfeld and Kothe[39] report a case of gangrenous appendicitis and hemorrhage from duodenal ulcer in a boy of ten. The white count was 190,000 with seven per cent. of myelocytes. From the above it is apparent that *infection*, particularly in children, may under certain circumstances give rise to unusually high relative and also absolute increase in the white blood cells as well as to forms of white cells abnormal in the blood.

Fractures are supposed in some instances to produce secondary leukemias. These are at times accompanied by peculiar blood changes. Simon[40] reports a case of an adult negro with fracture of the ankle and crushed leg. At first there was a polymorphonuclear leukocytosis. A week later the wound became septic; the spleen enlarged; the white count was 60,000, with fifteen per cent. of neutrophilic myelocytes, one and two tenths per cent. of eosinophilic myelocytes, and seventeen and five tenths per cent. mast cell leucocytes. A week later the blood was almost normal and three months later was entirely normal.

Cases of cancer reported by Kurpjuweit[41], and Kast[42] showed greatly increased numbers or the presence of many abnormal cells, chiefly myelocytes, in the blood and tissues. Various other conditions have been associated with leukemic-like changes in the blood, such as variola[43], hereditary syphilis[44], and also other types of syphilis, rickets, intestinal infections and tuberculosis[154, 155, 156]. Experimentally Dominici[45] produced myeloid changes in the blood in experimental tuberculosis, typhoid, sepsis and potash poisoning, although such changes are not comparable with those of primary leukemia.

This proposed division of leukemia into primary and secondary is on a less firm basis than the similar classification of the anemias, for in the so-called primary leukemias the cause is not established and even in the secondary or symptomatic leukemias the blood picture in only certain instances resembles that of leukemia. Such cases show abnormal elements which are for the most part myeloid changes in the blood. The marked response of the hematopoietic system in children in determining the so-called leukemic reaction is suggested[46, 47] to be related to the so-called status lymphaticus.

Physical Signs

The usual clinical aspects of the disease, leukemia, are familiar: the insidious onset, the enlargement of the abdomen, or the superficial glands being commonly first noted, the weakness, malaise, anemia and emaciation, or in the acute cases the symptoms suggesting infection-fever, stomatitis, angina, with or without hemorrhage. In the following pages the clinical picture of the three main types of leukemia will be described in detail.

CHRONIC MYELOGENOUS LEUKEMIA

Clinical Picture

The onset is gradual and insidious as a rule, the patient first complaining of a sense of weight or dragging in the abdomen, gastric disturbances, or pains in the left side, symptoms which are the direct result of the enlarged spleen with or without a perisplenitis. In some instances the patients themselves are the first to discover the enlargement of the abdomen, while others seek medical advice for weakness, loss of weight, pallor, vertigo, dyspnea, or gastro-enteric complaints (vomiting or diarrhea), which are the secondary symptoms of a progressive anemia of moderately severe grade. Occasionally the enlarged spleen is an accidental finding made by the physician in a routine examination. Hemorrhage from the nose or bowel is common at some time, usually in the later stages of the disease (five-sixths of Cabot's cases[5]), but rarely is it a dominant symptom. This is in sharp contrast to acute myelogenous leukemia where hemorrhages are frequent and a prominent symptom. The general appearance of the patient may be excellent except for slight pallor. Slight irregular fever with sweating is not unusually observed. A symptom, which we have noted very constantly in a series of leukemic patients, which has not been commented on before, is the tolerance of these individuals for cold even in the later stage of the disease when the weak patient was in an emaciated condition. Recent studies in basal metabolism, proving the marked increase of metabolism in leukemia, afford a satisfactory explanation of this tolerance for low temperatures. Chills occasionally are a source of annoyance to the patient.

In the early stages the symptoms may be no more severe than those described above and physical examination may reveal very little besides pallor and a very large spleen, reaching down into the pelvis in some cases. No swelling of the lymph glands can be made out at this period, as a rule. One or two years may pass with the patient in this condition but the general tendency is downward. In spite of periods of remission, spontaneous or induced by therapy, the progressive character of the disease manifests itself by an aggravation of all the symptoms of a severe secondary anemia. The pallor, weakness, sense of fatigue and loss of weight increase. The poorly nourished heart muscle gives rise to loss of compensation and hence increasing tachycardia, palpitation, dyspnea, cough, anorexia, flatulence and abdominal distension occur. The patient becomes bedridden, the temperature is frequently elevated, there is often sweating, while pain over the splenic area, hemorrhages, rapid emaciation, poor sleep and increasing asthenia indicate an early fatal outcome. Death usually results from general anasarca due to myocardial insufficiency or is brought about by an intercurrent infection. Occasionally exitus follows hemorrhage from nose or bowels, or into the brain.

Physical Examination

The results of physical examination may be grouped systematically as follows:

General Appearance.—The pallor of lips and mucous membranes is almost always noticeable and may be intense. There is more or less emaciation with prominence of the abdomen due to enlarged spleen.

Eyes.—The vision is rarely impaired, although retinal changes, located at the periphery of the fundus, are frequent. These lesions are white flecks with a red border, usually small, of irregular shape, sometimes striated and lying close to the vessels. They represent collections of leukocytes and degenerated nerve elements surrounded by traces of hemorrhage. Rarer findings which have been described are an involvement of the optic nerve with choking of the disc, a uniform opacity of the retina and hemorrhage into the vitreous. Cabot[5] met with two cases of unilateral exophthalmos.

Ears.—In the late stages deafness may be noted with Menières' syndrome of tinnitus and vertigo, due to involvement of the labyrinth. Parke-Weber described nine cases with hemorrhage into the labyrinth.

Nose.—Epistaxis is not uncommon and may be slight or severe.

Mouth.—The teeth may become loosened. The gums may appear swollen, spongy and bleed readily; necrosis may result with ulceration and gangrene involving the buccal cavity. Such lesions are characteristic of acute myelogenous leukemia, but are rare in the chronic form.

Throat.—The tonsils and lymphatic tissue of the pharynx are slightly affected as a rule, showing moderate swelling in some cases. Necrosis and severe gangrenous processes are usually limited to the acute cases. Leukemic infiltration of the larynx may cause severe dyspnea. The dyspnea in the great majority of cases, however, is due to myocardial weakness and the embarrassment due to abdominal distension.

Glands.—In the great majority of cases glandular enlargement is entirely absent or of only minimal degree. In the earlier stages it is practically never encountered though late in the course of the disease slight swelling of the lymph nodes and very exceptionally enlargements of considerable size are observed comparable to those in the lymphatic type of leukemia. Such nodes are painless, free from inflammatory reaction, do not coalesce and are freely movable on the underlying tissues. Compression phenomena (dyspnea and recurrent nerve paralysis) due to enlarged mediastinal glands and ascites due to masses of abdominal lymph glands have been reported by a few observers.

Lungs.—Chronic diffuse bronchitis is not an infrequent finding. As complications pleurisy and pneumonia are often seen. The dyspnea, as explained above, is the result of a failing heart muscle, with varying grades of pulmonary congestion, accentuated by the mechanical interference caused by abdominal distension and splenic enlargement tending to push the diaphragm upwards. The condition may also produce very obstinate and troublesome cough from basal edema. Hemoptysis is very rare.

Heart.—The findings in the heart are the usual ones in a secondary anemia, such as tachycardia, systolic murmurs, especially at the base and in the veins of the neck, and slight dilatation accompanied by the subjective symptoms and objective signs in the other organs which characterize myocardial insufficiency.

Spleen.—In the majority of cases the spleen appears as a massive tumor frequently filling more than half of the abdomen. The enlargement, greatest in long standing cases, takes place in a downward and forward direction as a rule. The enlarged spleen may reach below the left anterior superior spine down into the pelvis and the anterior border may extend beyond the midline, occasionally even as far as the anterior superior spine on the right. The form of the organ is preserved, so that one or more notches can often be felt, while its consistence is firm. Besides the dragging sensation of weight there may be pain or sensitiveness to pressure, the result of perisplenitis or infarction. Peritoneal irritation of this sort may cause a palpable or audible friction rub over the spleen and lead to spasm of the abdominal muscles. There is no relation between the size of the spleen and the total white count. The spleen may suddenly increase in size as a result of internal hemorrhage or become smaller under the influence of arsenic, X-ray, radium and benzol and frequently as a result of an intercurrent infectious disease.

Liver.—The liver is enlarged regularly but in varying degree; its edge is firm and smooth. Occasionally it may reach as far down as the umbilicus. There is no jaundice unless a complicating disease of the gall bladder or bile passages is present.

Digestive Organs.—Troublesome symptoms from the gastrointestinal tract such as anorexia, feeling of fullness, vomiting, flatulence, distension, etc., are common from the outset, but the only symptoms resting upon the pathological basis of leukemic infiltration of the gastrointestinal wall are hemorrhage and diarrhea, both of which tend to occur late in the disease. Hemorrhage from the bowel is more frequent than hematemesis. Autopsy may fail to reveal a lesion in some of these cases. Ascites has been frequently observed. The ascitic fluid is clear, contains many cells and as in the pleural exudate of leukemia these cells are in many instances myelocytes, eosinophils and mast cells. This is probably not the result of a mere transudate, but signifies a leukemic infiltration, such as has been described in the omentum.

Kidneys.—The leukemic process never causes palpable enlargement of the kidneys. Marked involvement, however, may be shown histologically in the form of a diffuse cellular infiltration without the appearance of albumin or casts in the urine. A large majority of cases, however, show either albumin or casts or both, seventy-five per cent. of Cabot's series. This probably does not signify that chronic nephritis exists in these cases.

The urine is generally normal in quantity, acid in reaction and the specific gravity tends to be high. The largest amounts of uric acid encountered in any disease are found quantitatively in the urine, which often gives rise to large sediments. Renal calculi from uric acid are relatively rare, however, and the occurrence of gout has only been reported four times.

Sexual Organs.—In the female, irregularities of menstruation are not infrequent. There may be menorrhagia, metorrhagia, or amenorrhea. Normal children have been born of leukemic mothers.

In the male, priapism occurs. Contrary to the general impression the percentage of cases showing this symptom is small. It is occasionally an early manifestation but most commonly a late one. Scheuer[48] reports thirty-six cases of leukemic priapism out of one hundred and forty cases of general priapism. Cabot[5] failed to meet with it in a series of eighty-nine cases of leukemia. Warthin[49] found it after death in three cases of myelogenous leukemia, and thinks it present in twenty-five per cent. of cases. According to Ruh[50] no case in the literature has been found which is due to lymphatic leukemia. The cause is a myelocytic thrombosis or infiltration of the corpora cavernosa. The duration may be from a few weeks to seven months; the condition is frequently accompanied by severe persistent pain of a dull boring character radiating to the lower abdomen. Micturition may be difficult or impossible, necessitating catheterization, which is apt to lead to cystitis. In a few cases sexual emissions and sexual feelings are retained. The priapism may disappear by organization and contraction of the thrombus, but as the onset is usually late in the disease the condition generally persists until the end. Surgical removal is dangerous because of the tendency to infection and the results from X-ray or radium therapy is not encouraging.

Brain and Spinal Cord.—Symptoms due to changes in the brain and spinal cord are comparatively rare, but when found are usually the result of either small or large hemorrhages, or of leukemic infiltration of nervous tissue. Cerebral hemorrhage, usually a later manifestation, may occur in multiple small foci, or as a single massive clot causing hemiplegia and even sudden death. Death from this cause is exceedingly uncommon, however, when contrasted with the frequency of death due to intercurrent infections. The process of infiltration or hemorrhage into the sheath of the cranial nerves occasionally causes a palsy, *e. g.* facial paralysis of this type has been observed. Deafness due to involvement of the eighth nerve has been mentioned before.

Cases with symptoms of spinal cord involvement proved by autopsy are rare. Stursberg[50] reports a unique observation of a typical case of chronic myelogenous leukemia of two years' duration in which sudden severe pain in the back occurred radiating to the legs. It was accompanied by a flaccid paralysis. Death followed in twelve days. Autopsy showed the symptoms to have been due to a hemorrhage into a mass of preformed myeloid tissue in the lumbar cord region pressing upon the dura. Histologically the cord showed an absence of any considerable cellular accumulation or hemorrhage, proving that pressure upon the cord and nerve roots was responsible for the paralysis.

The Skin.—Leukemic involvement of the skin is an exceptionally rare condition in the chronic myelogenous type of the disease, being more often observed in chronic lymphatic leukemia. Petechial hemorrhages into the skin and purpuric areas, especially toward the end of the disease, are relatively common.

Temperature.—There is almost always a slight degree of fever and even marked fluctuation either early or late in the disease, although there may be no temperature rise at all. The chart is not characteristic.

Blood Picture

As the blood flows from a small puncture in the ear or finger leukemic blood is not characteristic. In advanced cases with severe anemia the pale color is noticeable and in pulling apart cover glass smears the sticky nature of the blood due to the great increase in leukocytes may lead one to suspect leukemia. The hemoglobin content of the red cells is not reduced in the early stages, but diminution proceeds with the advance of the disease, so that readings of forty to sixty per cent. are usual, ending in severe anemia in the terminal stages. The total count of red cells follows as a rule very closely the fall in hemoglobin, so that when the patients are first seen the red cells are apt to lie between two and three million. The color index is generally low, as one would expect it to be in a secondary anemia. The red cells show variation in size, shape and staining reaction. Anisocytosis of slight grade is the rule with rather noticeable poikilocytosis. In severe cases megalocytes, such as one encounters in pernicious anemia, are found. Polychromatophilia and basophilic stippling are consistently observed, as are nucleated red blood cells. Normoblasts predominate but megaloblasts are also discoverable in some preparations of blood. Blood platelets are increased.

The outstanding feature of the blood picture, however, is generally the tremendous increase in the number of white blood cells, which often exceed several hundred thousand and occasionally pass beyond one million per cubic millimeter. Only a few cases are on record in which accurate blood examinations have been made immediately before the leukemic transformation of blood began while the white count was still low. Most of the reports in the literature dealing with instances of submyelemic values of total white cells have to do with cases in which the white count was primarily very high but had been reduced by X-ray or radio-therapy, or as the result of an infection. It is not the number of cells but the appearance of myeloid cells in the peripheral blood which is the significant fact in myelogenous leukemia. The total number of white cells is in no way considered as a basis for determining the severity of a case, yet, in a general way, the progressive increase in the count is usually an unfavorable sign and the patient is apt to feel less well, while rapid decreases in the white blood count from any cause are likely to be accompanied by an amelioration of the other svmptoms.

The essential characters of the blood smears follow:

1. In the stained smears we find that the increase is mainly in polymorphonuclear neutrophilic leukocytes. The percentage of these cells may

vary from thirty to eighty per cent., while their absolute number is greatly increased.

2. Polymorphonuclear eosinophilic leukocytes may vary from five-tenths to five per cent., sometimes showing no percentage increase but nearly always marked absolute increase.

3. Polymorphonuclear basophils (mast cells) may vary from three to twenty per cent. or even higher, giving both relative and remarkable absolute increases.

4. Large mononuclear transitional cells are not numerous as a rule but may be absolutely increased. When many myeloblasts are present it may be very difficult to always surely identify this type of cell.

5. Neutrophilic myelocytes, never present in normal blood, may appear in small percentages at first but later reach thirty to forty per cent. or higher. Their size is larger than that of the polynuclear cell and there are many variations in shape of the nucleus.

6. Eosinophilic myelocytes are also numerous. They contain acidophilic granules in part, while others contain basophilic granules as well.

7. Mast or basophilic myelocytes are usually present.

8. Myeloblasts are infrequent (one to three per cent.) in the typical picture, but are very variable. They occur in great numbers in acute exacerbations of chronic myelogenous leukemia and in the definitely acute cases.

9. Lymphocytes are greatly reduced on a percentage basis, but almost always the total number is increased. Too high values for lymphocytes are obtained unless one is careful to distinguish myeloblasts.

There may be frequent variations from the above picture in certain details. The polynuclear neutrophilic cells may all appear relatively smaller or larger than the normal cell. The nuclei may show all stages of the development from the oval nucleus of the myelocyte to the multi-lobed nucleus of polymorphic type. Metamyelocytes or unripe polynuclears are terms applied to these cells. The number of granules as well as their size is variable. There may be none or a few very coarse granules or numberless fine ones. Occasionally basophilic granules are found in neutrophilic as well as in eosinophilic cells. Myelocytes may be abnormally large or small. When myeloblasts are present careful scrutiny will usually reveal many cells with just the beginning stages of granulation, the stage in development between myeloblast and myelocyte, which can conveniently be termed premyelocyte.

To summarize, the most characteristic features of the blood picture are the large total numbers of myelocytes, eosinophils and mast cells, plus the presence of nucleated red cells.

Repeated examinations of the blood of the same case at frequent intervals will often show contradictory results. Thus for example at one period the myelocytes may represent over fifty per cent. of the white cells, but at another time later on be less than twenty per cent. The mast cells and eosinophils are subject to the same variations. It is stated by some authors that a higher mast cell count often accompanies an improvement of the clinical condition and that these cells are relatively least affected by X-ray therapy; their significance, however, is unknown. Of extreme interest is the sudden change, the enormous increase of myeloblasts, which in certain instances may take place in the blood picture of a chronic case just before death. This probably represents the terminal exhaustion of the bone marrow and the pouring out of absolutely unripe cells. There are considerable variations in the counts of myeloblasts made from time to time. Certain cases are myeloblastic from the start (see acute myeloblastic leukemia); others show the remarkable increase when the clinical condition becomes worse. When the percentage of these cells is large and there are relatively few myelocytes one may readily at first mistake myeloblasts for lymphocytes (for differentiation see acute myelogenous leukemia). Careful study will usually show, however, some very fine granules in cells which at first glance might be thought to contain none, *i. e.* all stages of transition from myeloblast to myelocyte can almost always be found.

Occasionally a myeloblastic leukemia develops upon a chronic picture following a remission induced by X-ray. These are the cases reported as showing a change from myelogenous to lymphatic leukemia. The clinical course and termination of the disease in many respects resembles that of chronic lymphatic leukemia.

CHRONIC LYMPHATIC LEUKEMIA

Clinical Picture

The disease begins so gradually that its exact time of onset rarely can be accurately determined. The accidental discovery of one or more painless swellings, or the enlargement of the tonsils, may be the first cause of the patient seeking medical advice. In other instances the individual may first complain of increasing weakness and loss of weight and it is the physician who discovers the presence of anemia with enlargement of the lymph gland and spleen. In cases where the anemia is of considerable grade some of the characteristic secondary symptoms may be found such as dyspnea, cough, palpitation, swelling of the ankles, headache, vertigo, tinnitus, general lassitude and gastrointestinal disturbances, none of which is in any way diagnostic of the disease. Hemorrhages into the skin, or from the nose, bowel, lung and genito-urinary tract may occur but are decidedly more often seen in acute types of this disease.

Physical Examination

Physical examination usually reveals pallor, general glandular enlargement, a spleen palpable or enlarged to percussion and a liver which as a rule is less markedly enlarged than in chronic myelogenous leukemia.

General Appearance.—Pallor of the skin and mucous membranes with more or less loss of weight is noted if the disease is moderately well advanced.

Eyes.—True leukemic infiltration is seen rarely in the eyelids. Lowenstein[52] reports a case of lymphatic leukemia involving the sclera. Symmetrical tumors were removed from the sclera, which histologically proved to be lymphoma. Physical examination was negative. The lymphocytes were thirty-six per cent. of the white cells of the blood. One year later the tumors recurred and were again removed. The lymphocytes now amounted to fifty-three per cent., and the physical examination was still negative. Four years subsequent to the second operation marked enlargement of the spleen and lymph glands was noted with local recurrence. The white count had risen to 2,000,000 cells and ninety-seven per cent. were lymphocytes. Disturbance of vision is rare but may occur as the result of retinal hemorrhage. The fundus may show "retinitis leukemica," small white flecks with a red border, a peculiar type of hemorrhage and occasionally blurring of the optic disk.

Ears.—Rarely deafness may occur due to lymphomatous involvement of the labyrinth.

Mouth.—Swelling and bleeding of the gums leading to gangrenous processes in the mouth may occur occasionally, but are more frequently seen in the acute cases.

Tonsils.—Considerable enlargement of the tonsils is not infrequent and this may lead to operative removal before the true nature of the disease is suspected. Severe hemorrhage and death may follow.

Glands.—Without question the most constant and important physical finding is the general and extensive glandular enlargement, which is rarely absent. The cervical, axillary and inguinal glands are usually involved, varying in size from a few millimeters to several centimeters in diameter. These lymph nodes are never the site of primary inflammatory changes, so that they exist as a rule in chains, separately, freely movable, not attached to the skin and showing no redness of the overlying integument. Matting together and breaking down, if it occurs, is due to some secondary infection. The consistence of the glands is firm; they are usually painless and rarely if ever tender on pressure. Although never occurring in the large symmetrical masses of a well established Hodgkin's disease, and rarely showing pressure symptoms, enlargement of the abdominal glands can occasionally be felt and involvement of the mediastinal glands may be determined by X-ray.

It is true that the more intently and systematically one searches for enlargement in all the lymph nodes of the body the more widespread the involvement is found, even though it be of very slight degree. Thus the epitrochlear, submaxillary and the chain of nodes reaching down the thorax from the axilla known as the "axillary tail" may be readily palpable in some instances. Cases of lymphatic leukemia without lymph gland enlargement have been reported but they are exceedingly rare. As a general rule the adenopathy is much more pronounced than in chronic myelogenous leukemia.

Heart.—There are as a rule no physical signs of specific leukemic changes in the heart demonstrable clinically. As the anemia develops signs of myocardial insufficiency may appear. At first tachycardia, palpitation and systolic murmurs at the base or in the vessels of the neck, may be found, followed in the later stages by increased cardiac dullness, relative insufficiency of the mitral valve with signs of congestion in the lungs and edema of the ankles and legs.

Lungs.—Some weeks or months after the onset of the disease pleural effusion may occur, possibly the result of mediastinal lymph gland enlargement. In the terminal stages edema of the lungs and bronchopneumonia are not uncommon. Pleural effusion of a milky character (chylous effusion) has been reported.

Liver.—The liver can generally be felt, its firm, smooth edge extending from one to four fingers' breadth below the costal margin and in occasional advanced cases it may appear as a massive tumor reaching to the umbilicus or below it. On the average, splenic enlargement tends to exceed hepatic. The liver function is apparently not involved although we have no reliable test of hepatic function comparable to the phenolsulphonephthalein test in determining renal function. Jaundice does not occur.

Spleen.—Enlargement of the spleen, recognized by palpation or by percussion, is present in practically every case and as a rule the firm edge can be felt reaching at least a hand's breadth below the costal margin. The average size is smaller than that encountered in chronic myelogenous leukemia but exceptionally one may find in the lymphatic variety the massive proportions which are prone to occur in the former type. In such instances the anatomic notches and smooth surface of the normal spleen are again preserved.

Digestive Organs.—Disturbances of the gastrointestinal tract may occur during the course of the disease but there are no characteristic clinical findings. Patients may suffer varying grades of anorexia, flatulence, nausea, vomiting, hematemesis, constipation, diarrhea and melena, which on the average are of a mild or transitory character. The presence of changed blood in the stool either macroscopic or shown by chemical tests points to leukemic infiltration of the gastric or intestinal wall. Ascites may occur as a terminal event, part of a general effusion into the serous cavities due to a decompensated heart or rarely when there is massive involvement of the retroperitoneal lymph glands.

Kidneys.—Palpable enlargement of the kidneys due to chronic lymphatic leukemia has not been recorded. The presence of albumin and casts is very common. Red blood cells are also found occasionally. These findings are not proof of a chronic nephritis. The urine is not remarkable otherwise except for the constant increase in uric acid which, however, is not as marked as it is in myelogenous leukemia where the larger number of white cells furnish more nucleic acid for its formation. Bence-Jones proteinuria has been reported by several authors (Askanazy[53], 1 case; Decastello[54], 2 cases; Boggs and Guthrie[55], 3 cases in myelogenous leukemia and 1 case in lymphatic leukemia; and Heimann, Wilson and Shaw[56], 1 case). It would seem, according to Boggs and Guthrie, that Bence-Jones proteinuria is not essentially dependent upon one disease but is a manifestation of bone marrow disturbance.

Sexual Organs.—Priapism which has been reported in myelogenous leukemia has never been reported in the lymphatic variety. In the female irregularities of menstruation may occur.

Central Nervous System.—True lymphomatous growths in the brain and spinal cord are rare. The cases reported of cerebral hemorrhage and leukemic infiltration of the nervous system are mostly of the myelogenous variety. Tumor formations especially in the orbit are more characteristic of the acute leukemia and the closely related chloroma. White[57] reports a case of lymphatic leukemia with combined degeneration.

Skin.—Lesions of the skin are common in chronic lymphatic leukemia. In twenty-six cases Hazen[58] found pruritus, prurigo, urticaria, bronzing, vesicles, pustules, localized infiltrations, nodules and tumors. In addition to finding these lesions in typical cases, where enlarged spleen, lymph glands and blood picture verify the diagnosis, leukemic changes are seen in atypical cases where there is little or no glandular or splenic enlargement and where the blood may be practically normal. Sections of such lesions will constantly show a lymphocytic infiltration of the leukemic type. These have been considered as instances of aleukemic leukemia. The term "leukemia cutis" is used to include all leukemic manifestations of the skin. Arndt[59] prefers the term "lymphadenosis cutis" and proposes the following three subdivisions: (a) aleukemic form if the blood is normal; (b) subleukemic form if the white blood cells are only slightly increased but the percentage of lymphocytes is decidedly above normal; and (c) the leukemic form when the blood picture is unmistakably that of lymphatic leukemia.

Hazen[58] found in sixteen cases of acute or subacute leukemia cutis that the skin lesions consisted of petechiae, nodules, vesicles, bullae, papules, maculopapules, pustules, hematomas and tumors.

Many of the cases of leukemia cutis reported by dermatologists are examples of the aleukemic, subleukemic or very slowly progressive type of leukemia. Thus Sweitzer[60] reports a case of universal leukemia cutis, a very rare form (the circumscribed type being the one usually met with), which was aleukemic for two years. The whole cutaneous surface was involved being thicker and rougher than normal with the face and the extremities showing the most marked change. There was slight glandular enlargement, the liver was palpable, the spleen not felt and the blood normal except for slight anemia. A portion of the excised skin showed marked acanthosis and dense infiltration of small lymphocytes. Two years later the findings in the physical and blood examinations were the same except that under X-ray treatment the skin condition had greatly improved. Sections of the skin at this time revealed the disappearance of the acanthosis and a marked reduction in the lymphocytic infiltration.

Bernhardt[61] reports seven cases of lymphatic leukemia or pseudoleukemia ranging from two to seven years duration with leukemia cutis, several of which were aleukemic. The percentage of lymphocytes varied from 50 per cent. to 84 per cent. Only one case was examined histologically postmortem. This showed typical changes in the liver, spleen and lymph glands. Skin sections were examined in five other cases and supported the diagnosis of leukemia cutis. Bernhardt classes the universal and partial erythrodermias, encountered in leukemia, as leukemia cutis. The first may simulate the picture of pityriasis rubra and the latter psoriasis.

It is evident, therefore, that there is a remarkable tendency to a great variety of skin lesions in lymphatic leukemia. These may occur in all types of the disease from the slowly progressive aleukemic variety to the acute fulminating type where the hemorrhagic tendency is constant. This will be discussed under acute leukemia. In the diagnosis of leukemia cutis one has to differentiate it from only one condition, *i. e.* mycosis fungoides. This may be done by the histological examination of a piece of the skin. In cases of leukemia cutis where the papules and small tumors coalesce the patient's face may take on the leonine appearance which has been described as one form of mycosis fungoides. Cases of this type are those described as lymphodermia perniciosa. The leonine or pseudoleprous appearance of the face in these cases naturally suggests the premycotic skin condition in granuloma fungoides.

Temperature.—Fever of slight or varying degree may be encountered during the course of the disease without the presence of any complication. It is in no way diagnostic. The more acute the case the greater the tendency to fever.

Blood Picture

The gross appearance of the fresh blood is not remarkable except that it may be pale, varying with the degree of anemia. The red blood cells are slightly or not at all reduced in the early stages but the average count when the patient is first seen is under three million which falls to a lower figure as death approaches. The occurrence of a remission is accompanied by a rapid rise in the red blood count sometimes to normal values. The hemoglobin content tends to parallel the red count and the color index is low as a rule. The number of leucocytes per cubic mm. of blood is on the average less than it is in chronic myelogenous leukemia, 180,000 compared with 410,000 (Cabot's series), and often the total count is below 100,000. Cases with higher counts are seen, however, though rarely exceeding one million. The blood platelets are said to be decreased.

The stained blood film, when the disease is advanced, shows the changes in the red cells of a severe secondary anemia. There occur nucleated red cells, normoblasts, more rarely megaloblasts, anisocytosis, poikilocytosis, megalocytosis, polychromasia and basophilic stippling. The appearance of the white cells is that of striking uniformity. The great majority of them, ninety-five to ninety-nine per cent., are seen to be practically identical with the small lymphocyte of normal blood. Careful study with properly made and stained cover slip preparations will show certain differences, however. Large numbers of these apparently normal cells are found to be practically devoid of the light blue protoplasmic border (Wright's stain) only a tiny rim being visible, and in some cases simply the naked nucleus remains. Where protoplasm is present the "azure granules" normally present in thirty to forty per cent. of lymphocytes are found to be diminished or almost entirely lacking. The nucleus of the pathological cell is often stained more lightly showing a looser and more delicate chromatin network than occurs in the dark staining, compact, round nucleus of the ordinary small lymphocyte. The leukemic cells may vary greatly in size and the small cells with naked nuclei predominate. A few cells with large pale nuclei and considerable protoplasm may be found in most cases of chronic lymphatic leukemia. Peculiarly lobulated nuclei (Rieder cells) are especially common in this disease. As a rule the larger type of lymphocyte is found in the acute cases, although some chronic lymphatic leukemias with predominance of the large lymphocyte have been reported.

The extreme fragility of many of the pathological lymphocytes is shown by the occurrence of protoplasmic masses in the smear. "Gumprecht shadows," which he considered degenerations, show the various stages of fragility and enable one to trace the process. The other leukocytes are generally relatively and absolutely decreased (polymorphonuclear neutrophils, eosinophils and basophils, and the large mononuclear and transitional forms). The blood of lymphatic leukemia does not give the guaiac or oxydase test nor does it show the presence of a peptic ferment.

Course of the Disease

Marked improvement in the clinical condition with subsidence of glandular swelling and splenic enlargement and accompanied by a remarkable change of the blood picture toward the normal may occur in three ways, *viz*: (a) spontaneously, without apparent cause; (b) through therapeutic effect of arsenic, X-ray, radium, or benzol; and (c) as the result of an intercurrent infection, especially where the infecting organism usually calls forth a polymorphonuclear neutrophilic leukocytosis. The total white count may fall to the normal level and the percentage of lymphocytes be greatly reduced although as a rule the relative proportion of these cells is higher than normal.

With almost no recorded exceptions the disease leads to death after a varying period of time. Cases may occasionally remain stationary in good health for years but in the end the progressive character of the disease asserts itself. The glands tend to grow larger and the percentage of lymphocytes is apt to be above normal. Gradually the anemia increases, accompanied by cachexia, weakness, dyspnea and the train of symptoms secondary to an anemia. In the late stages fever and the tendency to hemorrhage suggest the similarity to acute lymphatic leukemia. Death may result from complications, especially sepsis, which the patients seem to stand badly. This has been explained as being due to the suppression of the marrow function and the inability to react properly to the invading organism.

THE ACUTE LEUKEMIAS

The separation of the acute leukemias from the two well established chronic forms is not always easy and in some instances the dividing line is very indistinct, as subacute cases occur which bridge the gap between the typically chronic and acute cases. In general, however, the acute types of the disease present a stormy onset and the course is rapid, usually terminating fatally in a few weeks or months. It may be doubted if any truly acute cases last over six months. Instances of longer duration raise the question whether in these a chronic leukemia, existing for some time without symptoms, may not suddenly have developed an acute exacerbation, a not infrequent occurrence.

When it comes to the separation of the acute leukemias into two subsidiary groups of acute myelogenous and acute lymphatic leukemia even greater difficulty is encountered. The clinical picture and the course of the disease is practically identical in both, but in many instances a differentiation is possible by means of careful cytological studies and the newer methods of staining of the blood and tissues. There remains, however, a small group where the type of cell is so embryonic in character that one cannot surely decide whether the cell belongs to the myeloid or lymphocytic series.

The first case of leukemia running an acute course was described by von Friedreich[62] in 1857. The patient died two months after the onset of the disease. Ebstein[63] in 1889 described the clinical picture and A. Fraenkel[64] in 1895 called special attention to the pathological changes of the blood stating that acute leukemias were all lymphemias in which the increase in the white cells was almost, if not entirely, in the lymphocytes. From that date contributions to the literature of acute leukemia have been many, although the cases have been almost exclusively classified as acute lymphatic and indeed the existence of an acute myeloid leukemia was denied by the majority of writers until 1904.

In recent years it has become more generally recognized that an acute leukemia of the myeloid type is of more frequent occurrence than was formerly supposed. Undoubtedly many of the cases reported as acute lymphatic leukemia before the last decade would now be called myelogenous in the light of our present knowledge. It seems more reasonable to suppose that the acute myelogenous cases have been wrongly classified as acute lymphatic leukemia than to believe that the incidence of myeloid cases of the acute type has suddenly become greater. Indeed, a review of the more recent literature seems to indicate that acute lymphatic leukemia is actually the rarer disease.

ACUTE MYELOGENOUS LEUKEMIA

(*Myeloblastic Leukemia, Acute Myelosis*)

Clinical Picture

Not infrequently, following some infection such as a tonsillitis, a furuncle, or an abscessed tooth, the patient is taken suddenly ill with high fever, headache, general malaise and extreme prostration. The gums are frequently swollen, red and spongy, reminding one of scurvy. There is a marked tendency to hemorrhage. The tonsils are often much enlarged and may share in necrotic or gangrenous processes in the mouth. The regional lymph glands of the jaw and neck enlarge rapidly. The picture is so similar to that of an ordinary infection that the true nature of the process is frequently unrecognized and incision of such glands has been made for drainage. The pallor which is as a rule present and the swollen gums should arouse suspicion of a leukemic process and suggest a differential blood count. The white blood count alone is generally subleukemic in the early stages.

All of the above symptoms are not necessarily present in every case. Thus there may be the following types: (1) Severe ulcerative or gangrenous processes in the mouth accompanied by minimal hemorrhagic tendency with little or no lymph gland or splenic enlargement; (2) Cases in which the hemorrhagic diathesis is the most striking feature suggesting the symptom complex, purpura hemorrhagica or morbus maculosus Werlhofii, with hemorrhages into the skin and from the mucous membranes; (3) Cases of a less virulent type where lymph node swellings and splenic enlargement are the salient features; (4) Occasional rare instances where none of the foregoing symptoms is present but only fever and a high degree of anemia are evident. Before death, however, there usually occurs some trace of the scurvy-like process in the mouth, of the hemorrhagic diathesis or of the involvement of the lymph glands and spleen.

Physical Examination

As a rule the patients look very ill and the pallor of the skin and mucous membranes is noticeable. Hemorrhages in the fundus of the eye are common. The most frequent involvement of the ear is deafness with Menière's syndrome due to involvement of the labyrinth. Palsy of the cranial nerves may occur. The most characteristic lesions are in the mouth where the leukemic process often leads to swelling, ulceration and gangrene of the gums, the cheek, the pharynx and tonsils. The necrotic slough frequently progresses to the formation of large masses of foul smelling dead tissue. The necrosis may extend very deeply into the tissues producing noma, with ensuing hemorrhage of varying degree.

Enlargement of the lymph glands of the neck is rarely absent, especially if there is involvement of the mouth, although cases have been reported in which no glands could be felt. The other glands of the body, such as the axillary and inguinal, present as a rule only slight if any enlargement in contrast with the findings in chronic lymphatic leukemia and in some cases of chronic myelogenous leukemia.

There may be a pleural effusion, which is often bloody, or signs of congestion of the lungs from a weakened myocardium. The heart reveals the usual findings of secondary anemia, such as increased frequency and hemic murmurs. Pericardial effusion and pericarditis may occur. Enlargement of the liver of slight grade may usually be made out although it is frequently absent. The spleen is usually palpable but may not be felt. Massive enlargement is decidedly infrequent.

Vomiting, severe diarrhea and hemorrhages from the bowel may occur. The urine frequently shows albumin and casts. The bones may be sensitive to pressure, although severe pains are exceptional. Marked irregular elevation of the temperature is present in the great majority of cases, the more acute the case the stronger the tendency to pyrexia. The skin frequently shows petechial or larger hemorrhages and occasionally leukemic nodules or actual areas of necrosis.

Blood Picture

The blood examination usually reveals a marked anemia, with a rapid and progressive fall of the total red cell count and the hemoglobin. Variation in the size, shape and staining reaction of the red cells is frequent. In the severe cases basophilic granulation, normoblasts and megaloblasts may be found. The resemblance to pernicious anemia may be most compelling, especially when the total number of white cells is very low, a frequent occurrence at the very beginning of the disease and sometimes also occurring during the course. This leukopenia may be the result of a spontaneous change or be induced by a complicating infection.

If examined at the onset of symptoms the white blood count is practically always subleukemic, ranging from a few thousand up to approximately thirty thousand cells per cubic millimeter. In some instances the count rises rapidly from day to day, amounting to several hundred thousand but on the average the numbers do not reach the high figures of chronic myelogenous leukemia. A few cases, aleukemic through their entire course, have been reported.

The first glance at the stained blood film almost always gives the impression that the specimen is one composed of large lymphocytes and the superficial deduction will be made that the case is one of acute lymphatic leukemia. This undoubtedly explains the view held until quite recently that nearly all acute leukemias were of the lymphatic type. Closer scrutiny of the individual cells will often show, however, that the protoplasm of many contain a fine neutrophilic granulation in varying amounts. These cells represent the transition stages between the myeloblast and the myelocyte, and may be termed premyelocytes. Naegeli[6] lays great emphasis on their presence as a diagnostic sign of acute myelogenous leukemia. Myeloblasts, premyelocytes and myelocytes together form a large percentage of the white cells, ranging from 30 to 60 per cent. or even higher. Fully developed adult neutrophilic leukocytes may be scarce in contrast with the picture in chronic myelogenous leukemia. In some cases the neutrophilic granulation is poorly developed and absent in many cells. Other evidence of rapid and atypical cell growth is the frequent absence of eosinophils or basophils and the abnormal indentations in the nuclei of the myeloblasts, so-called Rieder cells. Occasionally the myeloblasts are of small size resembling the small lymphocyte of chronic lymphatic leukemia.

Naegeli[6] feels that the lymphocyte can be separated from the similar appearing myeloblast on certain finer morphological characteristics of the nucleus. According to his conception the myeloblast is a large mononuclear cell with deeply basophilic protoplasm which shows four or five nucleoli in a lighter azure staining nucleus. The lymphocyte differs from this cell in having a less basophilic protoplasm, a darker nucleus with only three or four nucleoli. It is not always possible for the average observer to decide the nature of isolated cells with these criteria. If, however, a given preparation is found to contain a few typical Naegeli myeloblasts, numerous myelocytes and premyelocytes, the remaining mononuclear cells of doubtful nature it is safe to conclude are probably members of the myeloid family. The oxydase reaction is a valuable aid in such instances.

The oxydase test as perfected by Graham[15] if positive in the large mononuclear cells of any acute leukemia is conclusive evidence of their myeloid nature and enables one to make the diagnosis of acute myelogenous leukemia. The more embryonic forms of marrow cells react negatively, however, so that only a positive result is conclusive. Cases of acute, large celled leukemia occur where nearly all the cells resemble large lymphocytes, none of the transition stage premyelocytes being present, and in these the oxydase test is generally negative. For decision one is here thrown back upon the purely morphologic characteristics of the cell, its nuclear structure, the absence of azure granules found in lymphocytes and the ordinary staining reaction. These cases form the battleground of hematologic discussion. The dualists of whom Naegeli[6] is the leader seek to differentiate myeloid and lymphoid cells even in this stage, while the unitarians headed by Pappenheim[8] consider these cases as "lymphoidocyte" leukemia, the cell representing an undifferentiated stage, the hemoblast, preceding both myeloblast and lymphocyte[14]. In some instances, however, even Naegeli admits that only the post-mortem histological evidence can make a decision possible.

Course of the Disease

The course of acute myeloblastic as well as acute lymphatic leukemia is usually rapidly fatal. In some rare instances remissions of short duration occur. The tendency to hemorrhage increases with the onward march of the disease. Intercurrent infections may cause a lessening or disappearance of the characteristic symptoms of leukemia and a change in the blood picture approaching normal although the termination of the fatal process is only slightly deferred. Cases of spontaneous recovery have been reported.

Differential Diagnosis

Undoubtedly many cases of acute myeloblastic and acute lymphatic leukemia have been recorded as other diseases where the clinical observation has been superficial and the careful examination of the blood and the tissues post-mortem have not been undertaken. Without such controls the diagnosis of scurvy, ulcerative stomatitis, quinsy sore throat, diphtheria, gumma of tonsil, sepsis, endocarditis, lymph gland tuberculosis, pseudoleukemia, pernicious anemia, hemorrhagic diathesis, and morbus maculosus Werlhofii may be wrongly made.

A diagnosis of acute myelogenous leukemia in order to be above criticism must be substantiated by proof of the following points: (1) an aleukemic or subleukemic stage; (2) an acute downward course with death usually ensuing in one to four months; (3) the characteristic blood picture of myeloblasts and myelocytes with the transition forms between the two; (4) the typical gross and histological findings in the liver, spleen, bone marrow and lymph glands; (5) the specific proof of myeloid elements by enzyme reactions.

There were only seven authentic cases in the literature up to 1903, according to Billings and Capps[65] who then reported their case, making eight in all; and although this number has been augmented since then there are still very few cases on record which fulfill all the postulates above laid down for establishing the diagnosis of acute myelogenous leukemia. In 1913 Naegeli, making a critical study, finds that the only instances on record where a subleukemic or aleukemic stage was noted are the following: (1) Billings and Capps[65], (2) Mager and Sternberg[66], (3) Hirshfeld and Alexander[67], (4) Naegeli[6], (5) Ziegler and Jochmann[68], (6) Wynhausen[69], (7) Herz[7].

One must further remember that an acute exacerbation of a long standing leukemia may lead to error. For this reason a short duration of symptoms is important in order to exclude a preexisting chronic leukemia. A case which illustrates this fallacy is reported by Panton and Tidy[70]. A typical chronic myeloid leukemia of long duration showed a myeloblastic change just before death. On November 28, 1911, myeloblasts were 7.6 per cent. and on March 12, 1912, myeloblasts had increased to 94.4 per cent. The authors believe this to be more common than supposed and therefore a possible source of error. Numerous similar examples have been reported.

The blood picture of all cases of acute myelogenous leukemia is strikingly suggestive because of the difficulty met with in classifying the large mononuclear cells. Some of these, the myeloblasts, are non-granular and look much like the ordinary large lymphocyte while others with a varying amount of granular protoplasm supply the transitional stages to the mature myelocyte. In addition a general variation of all the white cells from the normal type is observed, which point in itself is very strong evidence of increased or abnormal bone marrow activity.

Conclusive proof is lacking in many excellently studied cases because a complete autopsy with histological study of liver, spleen, bone marrow and lymph glands was not made. Myeloid change in these organs must be demonstrated microscopically before one can say the case has been proved to be acute myeloid leukemia. A slight myeloid change is not sufficient proof. It must be a marked transformation, since mild proliferation of myeloid tissue is not uncommon in severe anemias. The possibility of error in failing to insist on this point is well illustrated by several cases cited by Naegeli[6]. Morawitz[71] reports a severe anemia following a necrotic angina which lasted some time. Enormous numbers of normoblasts and megaloblasts were seen. The neutrophilic myelocytes numbered 20 per cent., the eosinophilic myelocytes 1 per cent. The total of white cells was 22,100. Considerable improvement followed transfusion, with ultimate return to a normal blood picture. On the clinical and blood findings scarcely anyone would doubt that the case was one of acute myelogenous leukemia, but since the patient recovered, one is forced to conclude that it was an anemia with a very active bone marrow. Simon[72] reports an interesting case of a fractured bone with coccus infection: white cells 50,000; neutrophilic myelocytes 15 per cent.; eosinophilic myelocytes 1.2 per cent.; mast cells 17.5 per cent.; erythroblasts 5.5 per cent. Recovery and normal blood picture followed amputation. Teeter reports a child of six years ill with fever and severe anemia: white cells, 130,000; erythroblasts 20,000 per cubic millimeter; myelocytes 11 per cent. Recovery.

Marshall[73] reports a case of acute miliary tuberculosis showing the blood picture of an acute myelogenous leukemia. The patient, fifty-two years old, was sick only five weeks with fever, weakness and chilly sensations. Increasing pallor, weakness and cyanosis led to an anemic death. Spleen and liver slightly enlarged. Glands negative. Blood culture negative. Red blood cells 1,320,000. White blood cells 23,840. Hemoglobin 20 per cent. (Sahli). Polynuclear leukocytes 42.5 per cent.; lymphocytes 4 per cent.; large mononuclears 18.5 per cent.; myeloblasts 2.4 per cent.; premyelocytes 1.8 per cent.; myelocytes 30.4 per cent. The total myelocytic forms being 34.8 per cent., clinically acute myelogenous leukemia seemed probable, Autopsy showed normal marrow with absence of myeloid change in spleen. liver and lymph glands. Instead, a miliary tuberculosis was discovered. Roth[74] describes a similar case. The reports of such cases testify to the necessity of autopsy and careful histological study for final and complete proof.

Last of all conclusive proof should be obtained of the myeloid nature of all cases by the application of the benzidin or the indolphenol blue synthesis test. If this test for oxydase is positive on blood or tissues there can be but one interpretation as to the nature of the cells which give it. There are indeed few cases on record which would pass a censorship so strict as that outlined. This emphasizes the need of more thorough and comprehensive study of all cases of acute leukemia.

ACUTE LYMPHATIC LEUKEMIA

The older view that all or nearly all acute leukemias are of this type is today rejected, as has been already stated, because of late years more complete study has shown an increasing number of these cases to be acute myelogenous leukemia. The great majority of acute leukemias occur in the early years of life, children and young persons forming the great bulk of all the cases. It has been reported in the new-born, in those at middle life, and even in the aged.

Clinical Picture and Physical Examination

Clinically the condition is characterized by the same subjective and objective findings which have been described under acute myelogenous leukemia, the same acute onset with fever, prostration, hemorrhagic diathesis, and ulcerative or gangrenous processes of the mucous membranes of the mouth being observed.

Blood Picture

The red cells and hemoglobin generally show the same evidence of a severe and progressive anemia as has been described in the acute myelogenous form. The total white count is low or even subnormal in the beginning, rising to 30,000 or 40,000 as a maximum, or reaching 200,000, or even 1,000,000 cells per cubic millimeter in some instances. As a rule, the counts are lower than in the chronic form, but no absolute numerical line of difference may be drawn. Some cases may be aleukemic during their entire course.

The first definite aid in differential diagnosis comes from the study of the leukocytes in the stained smear. Generally there is a marked increase in the percentage of lymphocytes, ranging from fifty per cent. to ninety per cent. or above. Often these are abnormal in type appearing as very large cells with pale staining nuclei which in many instances may show indented nuclei, so-called Rieder cells. Usually the large lymphocyte predominates but Rieder cells, and even the small lymphocytes, may play the leading role in an acute lymphatic leukemia. Azure granules may be absent or greatly increased in the large lymphocytes. Naegeli[6] states that small lymphocytes with azure granules are, in his experience, always or nearly always decreased and never increased. Auer[75] has observed small azurophil rods in the large lymphocytes (Auer bodies) of acute lymphatic leukemia. The percentage of neutrophilic and eosinophilic leukocytes, as well as their total number, is often greatly reduced. Myelocytes are rarely seen and when present are considered as a stimulation myelocytosis. They may reach ten per cent. but are often transitory.

The course of the disease is acutely and progressively downward, similar to acute myelogenous leukemia. The same disease pictures, from the standpoint of differential diagnosis, may be confused with acute lymphatic leukemia, as have been mentioned under acute myelogenous leukemia.

DURATION AND TERMINATION OF LEUKEMIA

Recovery, so far as is known, does not occur in true leukemia. Within the last eight years, however, apparent cures have been reported, but in these instances it is doubtful whether the authors were dealing with a leukocytosis, usually of the cells of the lymphocytic series, or leukemia. The various methods of treatment advocated, therefore, must be regarded at the present time as palliative measures to delay the fatal outcome either by inducing remissions or slowing the progress of the disease. The duration of the disease depends upon the type or variety of leukemia, the age of the patient, and probably upon the treatment adopted. Chronic leukemia, either myelogenous or lymphatic, may last months or years, on the average from two to four years. Certain exceptional cases are reported in which the duration of life was ten years after a positive diagnosis was made. It must be borne in mind, however, that a typical chronic case of myelogenous leukemia, as indicated by the blood picture and clinical findings, may at any time, with or without treatment, take on an acute rapidly fatal course. The blood also in these cases frequently changes to a condition similar, if not identical, to that found in acute leukemia.

The duration of acute leukemia, either of the lymphatic or the myelogenous type, is a few weeks, or months, on the average three to five weeks, from the onset of symptoms. The true onset of leukemia is very insidious, however, and the duration is, therefore, usually difficult to determine; thus the course may be somewhat longer than is usually believed. Acute leukemia rarely if ever changes into one of the chronic types, although occasionally such cases live for two or three months. Remissions in the disease may rarely occur spontaneously; they may, however, be induced by various therapeutic agents.

It is, in certain instances, very difficult to make the diagnosis between acute leukemia and leukocytosis due to infection. Cabot bases his opinion on the fact that in leukocytosis there is a less marked increase of leukocytes, and on the recognition of the infection to which the adenitis is secondary. Ruhrah adds that the amount of change in the red blood corpuscles is important, that is, in true leukocytosis there would be little change in the number, shape, or color of the red cells. Whereas, in true leukemia the change in the red cells may be slight but is usually marked.

Cases of infections about the throat with general enlargement of the lymph glands and a very high relative lymphocytosis and moderate to marked increase in the total number of lymphocytes have been described[5, 25, 76]. These cases entirely recovered. There is, however, very great doubt that they were really cases of true leukemia. Indeed, in two cases reported by Cabot[5], already referred to, in which the relative lymphocyte counts were sixty-four per cent. and sixty-six per cent., and the total white count 185,000 and 94,000, the patients proved to be suffering from whooping-cough and pneumonia. From the preceding and numerous other and similar instances it seems very doubtful if these cases can be considered as leukemia in which recovery occurred.

A low white count may occur in leukemia at the beginning, at the end, or any time during the course of the disease. Such aleukemic phases may be without known cause. They may be the results of various kinds of treatments, or of such intercurrent diseases as pneumonia, diphtheria[77], erysipelas[78].

The prognosis in leukemia depends on the acuteness or chronicity of the disease and not whether it is of the lymphatic or myelogenous type. Clinically the acute types do not differ very much from each other. Although the duration of life in chronic leukemia in a series reported by Giffin[79] averaged two and a half years, exceptional cases lived nine and one-half years and one case was of ten years and seven months' duration. Chronic leukemia, however, may terminate by conditions similar to the acute form of the disease. Such acute terminations of chronic leukemia are reported by numerous authors[78, 80, 81, 82].

Pathological Anatomy and Histology

The pathological anatomy and histology of the three main types of leukemia will be described separately in the following pages.

Chronic Myelogenous Leukemia

The characteristic post-mortem findings of the leukemic process are confined to the blood and the blood forming organs. The other tissues of the body show the secondary effects of a severe anemia (pallor and increase of fat), accompanied by much less striking evidence of leukemic infiltration; this latter change can, as a rule, be only determined microscopically. The blood when clotted may appear greenish white and petechial hemorrhages may be found in various organs.

Spleen.—The enlargement of the spleen is remarkable; its huge bulk extends in some cases well down into the pelvis. It may weigh from two to ten kilograms. The normal shape of the organ is retained and the notches are accentuated. Its surface is smooth and frequently of a gray or grayish white color due to the fibrous thickening of the capsule and to areas of perisplenitis with adhesions which often bind the organ to adjacent structures. The consistence of the spleen is increased, due to the proliferation of the fibrous tissue in the stroma, the trabeculae and the capsule. On cut section the color varies from grayish red to a reddish tint, depending upon the amount of fibrous tissue present; the surface is finely granular and opaque. Where the fibrous tissue is excessive, the consistence is exceptionally firm and the color is a decided uniform gray. The Malpighian bodies are not visible. Infarcts are not infrequently found and areas of hemorrhage may be noted. If accessory spleens are present they, too, share in the enlargement.

Microscopically the spleen has lost its normal architecture and is closely packed with masses of cells which, as a rule, have obliterated the well known landmarks, the Malpighian bodies, although the delicate venules of the splenic pulp, with their wall of a single layer of endothelial cells, may still be readily recognized as intact. A great variety of cells comprises the infiltrating horde and fills the intervening pulp tissue as well as the venules. Neutrophilic and eosinophilic myelocytes predominate, but there are found in large numbers neutrophilic, eosinophilic, basophilic leukocytes. basophilic myelocytes, myeloblasts and red blood corpuscles. Nucleated red cells are present but are relatively few in proportion to the other types of cells encountered. The giant cells of the bone marrow, megalocaryocytes, are commonly met with in small numbers. One may find cells of the myeloid series and nucleated red cells in the actual process of migration through the interstices in the endothelial wall of the blood vessels. The increase of fibrous tissue is seen especially along the walls of the sinuses and capillaries which may show hyaline changes.

Bone Marrow.—In its gross appearance the bone marrow shows a striking change, the normal bright yellow "fat marrow" in the shafts of the long bones being replaced, as a rule, by a firm homogeneous, pale, yellowish gray or pinkish gray tissue. In some instances traces of the original "fat marrow" remain and in exceptional cases the marrow may have a greenish tint resembling the deposits seen in chloroma.

Microscopically the picture of cellular hyperplasia bears a striking resemblance to that already described in the spleen. It consists of a mass of cells among which one can with difficulty differentiate the vascular channels composed of a single layer of endothelium. The predominating cell type may be the neutrophilic myelocyte, the eosinophilic myelocyte, or the myeloblast. There are present also in great profusion leukocytes of all kinds, basophilic myelocytes and to a less extent red corpuscles. Normoblasts are present in small numbers contrasted with the finding in pernicious anemia, so that the erythroblastic tissue appears to be submerged and displaced by the hyperplasia of the myeloid cells. The fully developed red cells are contained mostly within the vascular channels whose walls are apparently quite permeable to the passage of cells of all types. The myeloblasts occur in greatest numbers outside of the capillaries. Myelocytes in the process of mitosis are not infrequently observed. Megalocaryocytes are present in small numbers.

Lymphatic Glands.—Gross enlargement of the lymphatic glands is generally absent, but when present is prone to be of slight degree and widely distributed, in striking contrast with the condition found in chronic lymphatic leukemia. In spite of the negative gross appearance of the glands, various grades of myeloid transformation may be found histologically. In some there is no evidence of pathological change, others show slight infiltration and still others may have assumed a character similar to that described in the spleen so that the normal lymph follicles are obliterated by the mass of myeloid cells and the cells derived from them.

Liver.—Notable symmetrical enlargement of the liver is constantly found, the weight of this organ varying from two to six kilograms. The surface is smooth, the consistence firm, but otherwise it presents no remarkable gross changes except for occasional small hemorrhages under the capsule in some cases. Microscopic examination shows the capillaries distended with masses of myeloid cells similar to those occurring in the spleen and marrow. Very few if any of these cells are actually outside the capillaries, although in places they may appear to be so when as a result of the pressure exerted by the overdistended capillaries entire strands of liver cells atrophy or disappear leaving a fused group of capillaries. Slight infiltration with myeloid cells may be found in the periportal connective tissue.

Other Organs.—The heart, lung, kidney, adrenal, thyroid, ovary and other organs are, as a rule, devoid of characteristic macroscopic evidence of the disease. Histologically the degree of myeloid change varies in the different organs and in different cases. It consists essentially in a filling of the capillaries with myeloid cells and occasional small linear collections of these cells parallel to and outside of the blood vessels.

This description, with one exception, applies to the changes in the central nervous system which are generally microscopic in character and so insignificant as not to have caused clinical signs. The occurrence of cerebral hemorrhage is a not infrequent finding, often too small to produce localizing signs, but yet extensive enough in some cases to cause death. Actual myeloid infiltration of the brain or spinal cord with destruction of nerve fibers which give signs during life are very rare, although such cases have been reported.

Fatty changes which are in general proportional to the degree of anemia may be observed in all the organs. These may be particularly well shown histologically by the application of such special fat stains as Scharlach R, Sudan III, or osmic acid.

Chronic Lymphatic Leukemia

The post-mortem findings and the histology of chronic lymphatic leukemia form, as a rule, a very characteristic picture.

Glands.—A general enlargement of all the lymph glands is usually present and readily visible to the naked eye. The glands are found to lie singly or in chains and only exceptionally are they matted together. They vary in size from that of a bean to a small hen's egg. On section the cut surface is smooth, homogeneous, soft, grayish white or reddish gray in color with an occasional small hemorrhage. Histologically the lymph gland may be scarcely recognizable because of the distortion of its normal architecture by the enormous numbers of infiltrating lymphocytes which tend to obscure the follicles and their germinal centers. The sinuses and capillaries if discernible are seen to be dilated and filled with lymphocytes. The vessel walls are often sclerosed. Small lymphocytes predominate in the chronic cases but, nevertheless, a certain number of larger lymphoid cells are almost always found.

Thymus.—The thymus is usually large and may even show tumor-like nodules and infiltration of the surrounding tissue. Histologically the change is comparable to that found in the lymph glands.

Spleen.—The spleen rarely reaches the size of that in the chronic myelogenous form of leukemia but regularly shows enlargement, symmetrical in character, with the preservation of the characteristic notches and the smooth surface. Often the capsule is thickened by a perisplenitis. The cut surface is generally grayish red or dark red in which the follicles occasionally are visible as grayish points. The consistence of the organ is not as a rule much above normal but may be increased in cases of long standing due to an excess of fibrous tissue. Infarcts are not uncommonly encountered. There is a remarkable alteration in the microscopic appearance of the spleen. The normal landmarks are, as a rule, completely lost being entirely replaced or almost wholly obliterated by a diffuse infiltrating mass of cells which are of a single type, lymphoid cells. The Malpighian bodies appear continuous with the dense uniform masses of lymphocytes and one discerns with difficulty the venules and interspaces of the splenic pulp which are lost in the homogeneous infiltration of lymphatic cells. In cases of long duration there is a tendency to proliferation of fibrous tissue between the venules.

Bone Marrow.—The normal yellow or fat marrow of the long bones is replaced by a dense cellular tissue of a gray or grayish red color which is as a rule homogeneous but may rarely show nodular areas visible to the naked eye.

Microscopic examination reveals almost complete substitution of lymphoid cells for the normal myeloblastic and erythroblastic tissue but in some cases there may remain isolated areas of both types of the normal marrow cells.

Liver.—The liver is enlarged generally and its markings are clearly made out on the cut surface. Histologically this is seen to be due to the nodules of lymphocytes gathered about the vessels in the periportal connective tissue. These nodules sometimes are sharply defined, in other instances they taper off between the strands of liver cells. The vessels are not remarkably dilated but contain numerous lymphocytes.

Kidney.—The kidney may show grayish linear markings due to infiltration of lymphocytes. The pelvis of the kidney may contain diffuse leukemic deposits which may be hemorrhagic. Histologically the same characteristics prevail as have been described in the liver.

Lymphatic Tissue Other than Glands.—The tonsils as a rule are quite large. The changes in the intestine consist usually in slight swellings of the lymph follicles and patches. Histologically the same transformation already described occurs, *i. e.*, lymphocytic infiltration.

Other Organs.—Leukemic deposits are occasionally found in the larynx, trachea, skin, nerves and meninges, and histological evidence of lymphoid infiltration has been recorded in practically every organ and tissue in the body. The more painstaking and careful the histologic study, the more diffuse and all-embracing will be found the leukemic process.

There is a remarkable tendency to accumulations of lymphoid cells about the blood vessels in the various organs and tissues, and in certain instances this accumulation is very marked beneath the endothelium of the smaller veins. Occasionally there is actual loss of continuity of the endothelium so that these groups of lymphocytes are potentially within the smaller veins. This histological appearance of invasion of the blood vessels by masses of lymphocytes suggests the possible explanation of the mode of transition from the subleukemic to the leukemic stage of leukemia. A similar condition is common in the lymphomata and leukemias of fowl and mice.

Acute Myelogenous Leukemia

The gross pathological findings do not vary materially from those of chronic myelogenous leukemia; the spleen and liver are smaller as a rule but may be greatly enlarged. The tendency to general hemorrhages and to ulcerative processes in the mouth is greater. Glandular enlargement is variable in extent and degree but is usual in the cervical region.

The bone marrow is generally grayish or red but sometimes even the normal yellow fat marrow is encountered in the long bones. The small nodules seen in lymphatic leukemia are never observed[6].

The only irrefutable evidence that a case of acute leukemia is one of the acute myelogenous type is obtainable from the histological study of the type of cell undergoing hyperplasia in the tissues. In typical cases there is a suppression of lymphoid cell activity and a diffuse hyperplasia of the bone marrow elements in spleen, lymph glands, liver and bone marrow. The spleen shows a marked infiltration of the pulp with myeloblasts, premyelocytes and myelocytes, the normal architecture being distorted and the Malpighian bodies being encroached upon or obliterated, leaving only the small arteriole as evidence of a previously existing splenic nodule. The lymph glands share in the same type of hyperplasia which is more dense toward the center of the glands but here also the lymph follicles are compressed and show no signs of activity in the central cells. The myeloblast is usually the predominating cell in all the organs.

The capillaries of the liver are distended with bone marrow cells and one finds areas of infiltration in the periportal tissue, or occasionally compression of the strands of liver cells by dense myeloid infiltration outside of the capillaries, forming microscopic leukemic nodules. In the bone marrow there is a great increase in the number of myeloblasts, premyelocytes and myelocytes at the expense of the red cells.

The application of the oxydase test to the tissues as well as to the blood may give important confirmatory evidence in diagnosis. The myeloid cells reacting positively appear in sharp contrast to the lymphatic elements present. Here again a positive test only is conclusive as very young myeloblasts may not react. The demonstration of a proteolytic ferment will also add further proof of the myeloid nature of the tissue in any specific case.

Acute Lymphatic Leukemia

The gross post-mortem findings show only slight variations from those of chronic lymphatic leukemia. The spleen and lymph glands are, as a rule, less enlarged and may even appear normal in size, although this is by no means invariable. There are frequent hemorrhagic, infiltrative and necrotic processes in the gums, mouth and tonsils, as noted clinically. As a rule, the leukemic change is one of diffuse infiltration but small gray nodules of leukemic cells or even large tumor-like leukemic nodules, may be observed in various organs of the body. These nodules are sometimes so striking as to lead to the diagnosis of lymphosarcoma. There seems to be no connection between the type of cell and the tendency to nodular growth, as both small and large lymphocytes seem capable of producing tumor nodules or diffuse infiltration, as the case may be. The tendency to hemorrhage in various organs should be emphasized. The bone marrow is usually dark red but in some instances much normal fat marrow may be preserved in the long bones.

Histologically one sees in these cases a gradual line of transition from the picture of chronic lymphatic leukemia with a tendency toward the preponderance of large lymphocytes as the infiltrating cells. Many cases of typical acute lymphatic leukemia, however, may show few or no large lymphocytes in the tissues[6], the cells all being of the small type as they may be in the blood during life.

The blood forming organs all share in a diffuse infiltrative process in which huge numbers of lymphocytes greatly obscure the normal structure. The spleen may show only diffuse lymphatic tissue with here and there a Malpighian follicle recognizable as such. The same process is found in the lymph glands. Only occasional germinal centers and lymphatic cords can be recognized. The infiltrating cells are found to be large and small lymphocytes, many of which show a typical structure. In some cases there is suggestion of true tumor growth, with infiltration and penetration of the capsule so that surrounding structures are involved.

The liver may contain true lymphomatous nodules in some cases. In the bone marrow there may be a diffuse or localized nodular involvement with lymphocytes; the red cells are usually decreased with actual aplasia of the myeloid elements, and groups of lymphocytes between the fat cells appear in the fat marrow of the long bones.

A diffuse infiltration of all the other lymphatic structures, such as thymus, tonsils and intestinal nodes is present in varying degree. Infiltrations have been described in practically all the organs of the body.

PATHOLOGICAL PHYSIOLOGY, CHEMISTRY AND IMMUNOLOGY

General Metabolism

Von Moraczewski[83] in a study of chronic leukemia concluded that leukemia is a nitrogen and phosphorus disease and found that almost all constituents in the food, especially phosphorus and nitrogen, were retained abnormally because of a lack of katabolism.

In "splenomedullary leucocythemia" Milroy and Malcolm[84] likewise observed an absolute diminution of phosphorus excretion. These observers also noted that the proportion of alloxuric nitrogen (uric acid and bases) to total nitrogen was increased. Later in "lymphatic leucocythemia" they found a marked diminution in the absolute amount of phosphorus excreted. In the case, which they studied, the uric acid and bases were hardly affected. In a case of "medullary leucocythemia," where the number of leukocytes was rapidly falling, the phosphorus excretion was found to have undergone no diminution while the uric acid and the bases were diminished. White and Hopkins[85] observed no relation between leukocytosis and the excretion of the products, such as phosphorus and alloxuric bodies, which result from katabolism of nuclein.

In complete balance experiments with cases of lymphatic and myelogenous leukemia, Stejskal and Erben[86] found in one case of chronic lymphatic leukemia a marked nitrogen retention indicating, according to them, diminished power of oxidation. In the case of myelogenous leukemia there was a slight retention of the nitrogen and phosphorus. Y. Henderson and

Edwards[87] in a case of lymphatic leukemia which they studied over a long period (six and one-half months) found that, notwithstanding a marked leukocytosis (175,000 to 380,000 per c. mm., 96 per cent. lymphocytes) and in spite of alternation of periods of great increase and marked diminution in the number of circulating corpuscles the excretion of phosphorus and uric acid was at no time excessive. They believe leukocytosis to be due not to general increase in nuclein metabolism, but to failure in normal destructive metabolism. In the course of their study they observed two periods: in the first, nitrogen was subnormal, uric acid slightly above normal, and phosphorus distinctly subnormal; in the second period there was a distinct diminution of nitrogen, an increase of uric acid, and a further great reduction in phosphorus.

Henderson and Edwards[87], by the changes in the amount and the proportion of urinary constituents during their own much more protracted observations, harmonize the conflicting observations of Milroy and Malcolm[84], von Moraczewski[83], and White and Hopkins[85] by showing that their apparent differences are probably due to the fact that these experimenters made their observations at different stages in the progress of the disease. Symmers[88] found the excretion of organic phosphorus in the urine pronounced in lymphatic leukemia.

Basal Metabolism

Murphy, Means and Aub[89] studied by calorimetric observations the basal metabolism in a man with chronic lymphatic leukemia. Observations were made in this case before and after X-ray and also after exposure to radium. The patient was studied five times in the respiration chamber. When first observed the metabolism was 44 per cent. above the average normal, falling a little with rest in bed. Intensive treatment by Roentgen rays caused a drop in the leukocyte count but did not appreciably affect the level of the metabolism. Water elimination through the skin and respiratory passages was unusually high. Direct and indirect calorimetry gave total results which were almost identical and no abnormal respiratory quotients were found. After treatment with radium a further very marked fall occurred in the leukocyte count, and at the same time there was a slight fall in the basal metabolism.

Other investigators[90, 91, 92, 93] have shown that in both forms of leukemia there is invariably a marked rise in the basal metabolism expressed in terms of body surface area. The average increase over the normal in eight cases of lymphatic leukemia was 52 per cent. and in five cases of myelogenous leukemia 44 per cent. The cause of the increase is uncertain. Grafe[90] believes it is due to active metabolism of large numbers of premature white blood cells. This is based on experiments with Bohr's blood gas pump or Haldane-Barcroft blood gas analysis apparatus. The oxygen demand of the total number of leukocytes in the body might form as much as 10 per cent. of the patient's total oxygen requirement. The intensity of rise in the basal metabolism is parallel, according to Grafe, with the clinical severity of the disease.

From the above it will be seen that the metabolism of leukemic blood is more active than that of normal blood. The nitrogenous balance is usually negative in acute and is variable in chronic leukemia. The endogenous uric acid elimination and the uric acid content of the blood are usually increased. There is often retention of phosphates.

Effect of X-ray on Metabolism in Leukemia

X-ray may or may not have a pronounced effect on the metabolism of leukemia. When it does, this effect consists of increased elimination of nitrogen, also of uric acid, the latter, however, returning to a normal figure as the leukocyte count approaches normal. When the leukocyte count falls as the result of irradiation there is some evidence to show that the basal metabolism falls coincidently.

In a case of myeloid leukemia treated by Roentgen rays Lossen and Morawitz[94] found that the volume of urine was diminished, that the total nitrogen, uric acid and phosphorus excretions were lowered and that the number of leukocytes was diminished (350,000 to 212,000). On continued treatment the uric acid content decreased, the nitrogen elimination remained the same and the phosphorus content increased. Koniger[95] in myeloid leukemia found that under the influence of Roentgen rays the uric acid excretion increases parallel with the retraction of the spleen and the breaking up of the leukocytes and that the uric acid excretion is a positive measure of cell breakage. Ammonia and phosphates show, at times, an increase generally parallel with nitrogen increase and also with the betterment in the leukemic symptoms.

In a metabolism study of leukemia under the influence of Roentgen rays, Musser and Edsall[96] found that the phosphorus metabolism is of particular interest. In conditions where leukemic symptoms are progressing there is a constant construction of tissues that are rich in phosphorus and, hence, they believe there will be a retention and since leukemic tissues contain large amounts of phosphorus the retention is relatively large. The excretion of nuclein products of disintegration of uric acid, purin bases and phosphates is likely to be high, due to a large amount of nucleins in leukemic tissue. By the influence of Roentgen rays in three-day periods the nitrogen excretion increased about 70 per cent., the uric acid about 60 per cent., the purin bases about 260 per cent., and the phosphates about 200 per cent.

The authors explain this action of Roentgen rays as due to accelerating autolysis.

Effect of Radium on Metabolism in Leukemia

We have been interested in the constitutional reactions which in certain instances followed the application of radium. These reactions were particularly marked in cases of cancer with suppuration such as carcinoma of the cervix and in cases of leukemia which had undergone prolonged radiation.

Levin[97] has also noted that in certain instances treatment of leukemia by X-ray and radium may at the beginning give rise to headache, nausea, vomiting, diarrhea and rise in temperature. These constitutional symptoms have also been described as occurring in normal individuals subjected during their routine work to the radiations of radium.

These general symptoms consisted of nausea, more rarely vomiting, malaise, weakness, even prostration, headache, undue fatigue, unusual need of sleep, increased excitability, fretfulness, irritability, disorders of menstruation and attacks of dizziness. Such symptoms are, however, common in many people at times and, as they cannot be accurately and objectively recorded, there is doubt if they can be proved in the majority of cases to be definitely due to exposure to radium. Such symptoms may be due to close confinement, tiring routine, lack of outdoor exercise and other causes. General symptoms undoubtedly do occur as the result of radiation from radium and they are analogous, indeed appear identical, to those produced by massive doses of Roentgen rays. For detailed literature, discussion and interpretation of this intoxication, reference should be made to the recent excellent and suggestive paper of Hall and Whipple[98].

Considering that toxic products from tissue autolysis might be responsible for the general symptoms following radiation by radium and that such disturbed metabolism might be indicated by changes in the urine and blood a preliminary study was made in 1913 and 1914, in association with Hammett and Harris, in cases of leukemia treated by surface applications of radium for in such cases the remarkable phenomenon of the complete disappearance of the enormously enlarged leukemic spleen by autolysis should be manifested by changes in the metabolism. At this time a marked increase in the products of nitrogenous metabolism was found in the urine.

In 1915 a similar but more detailed study of another case of advanced myelogenous leukemia was reported by Ordway[99] and Knudson[100]. Not only was the amount of total nitrogen, urea and ammonia found to be markedly increased immediately after the action of radium as in the preliminary work above referred to but the phosphates increased as high as 400 per cent. over the examination at the beginning of treatment.

The urine analyses in a case of myelogenous leukemia treated by radium are recorded in Fig. 3. On observing this chart it is seen that after the first series of radium treatments the total nitrogen, urea nitrogen and ammonia nitrogen began to increase immediately; at the end of seven days the excretion reached a maximum and was more than double. After the

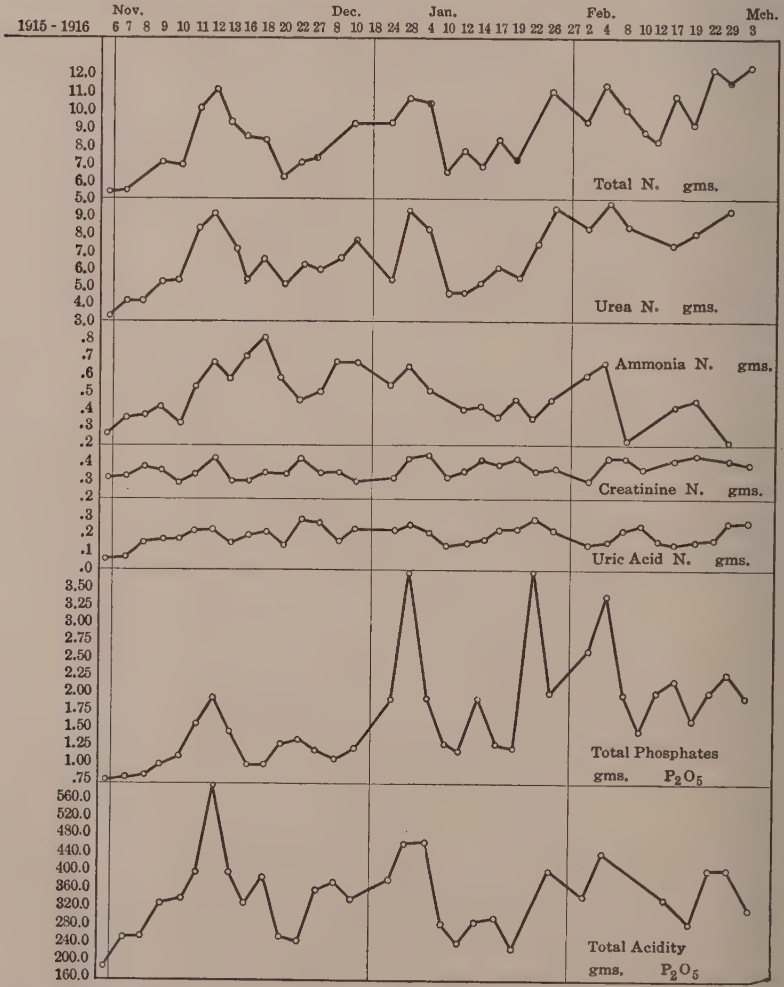


Fig. 3.—Case I. Myelogenous Leukemia, chart of analyses of urine during radium treatment. Taken from article by Ordway, Tait and Knudson, *Albany Medical Annals*, 1920, XLI, 1.

seventh day there was a slight decrease and then it remained more or less constant. The uric acid output showed a slight increase for the first seven

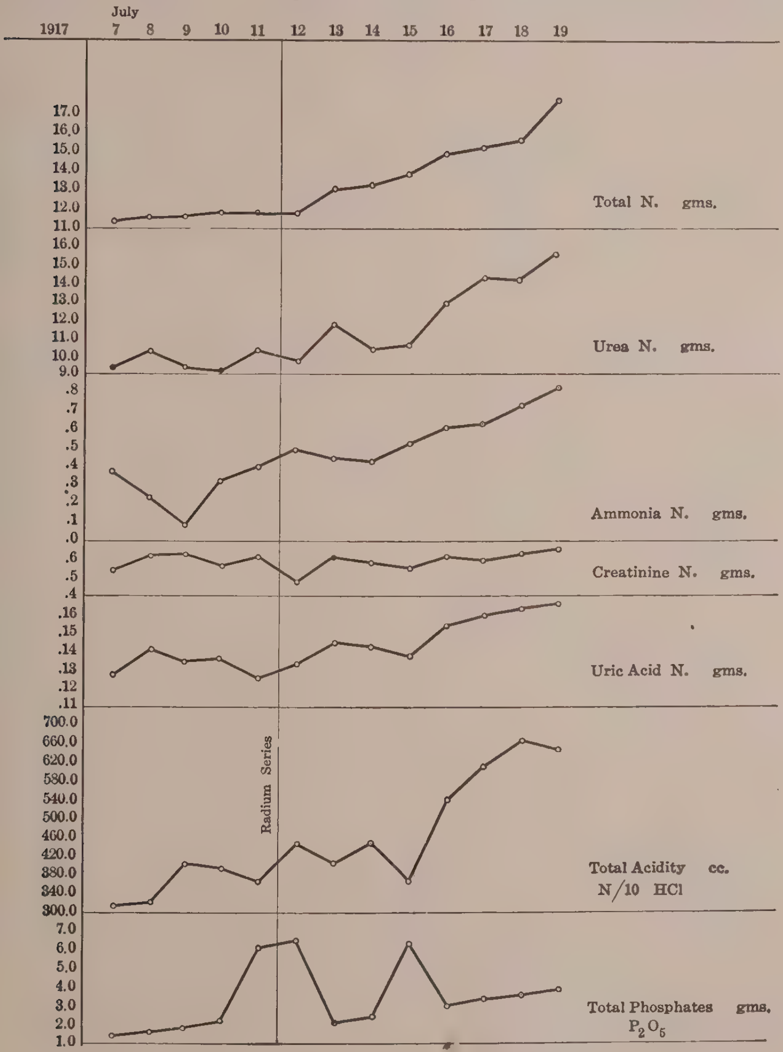


Fig. 4.—Case II. Myelogenous Leukemia, chart of analyses of urine during radium treatment. Taken from article by Ordway, Tait and Knudson, *Albany Medical Annals*, 1920, XLI, 1.

days and then remained about the same. The elimination of total phosphates showed a most remarkable result. Phosphates increased immediately; after the seventh day of treatment there was a gradual fall toward the next series of radium treatments. The fall did not reach normal but remained about twice this amount. After the second series of radium treatments the total nitrogen, urea nitrogen, ammonia nitrogen and uric acid showed a similar increase in excretion for six or seven days. The phosphate excretion was likewise increased. After the third series of radium treatments the increased excretion of the various substances above mentioned was similar. It is interesting to note that after all three series of radium treatments the increase in excretion continued for about six or seven days after the beginning of treatment and then dropped. The phosphate elimination showed the greatest increase.

In another case of myelogenous leukemia examination of the blood before, during and immediately following radium treatment showed on July 7, 1917, creatinin 1.5 mgm. per 100 c.c., non-protein nitrogen 28 mgm. per 100 c.c.; July 14, 1917, creatinin 1.14 mgm. per 100 c.c., non-protein nitrogen 33 mgm. per 100 c.c.; July 19, 1917, creatinin 1.04 mgm. per 100 c.c., non-protein nitrogen 30 mgm. per 100 c.c. This result shows that there is apparently no change in the amount of creatinin in the blood and possibly a very slight increase of non-protein nitrogen during radium treatment.

The chemical examination of the urine in this second case is recorded in Fig. 4; during radiation there is a very marked increase in the volume of urine. The specific gravity remains constant. The total acidity is enormously increased as is also the ammonia nitrogen, total nitrogen, urea nitrogen. The creatinin shows no change. The uric acid nitrogen is slightly increased and the phosphates are enormously increased. The results, therefore, are in entire conformity with those of Case I, Fig. 3.

It seems evident that the changes in the nitrogenous metabolism depend upon the amount and nature of tissue autolyzed. Both the tissue autolysis and the products of nitrogenous metabolism are marked in the two cases of leukemia, Cases I and II. In these two cases also the phosphates show an extraordinary increase due to the nature of the tissue autolyzed. In a case of sarcoma the bulk of tissue autolyzed was obviously less than in the cases of leukemia but following radiation there was definite softening and fluctuation of the growth. The nitrogenous products in this case while definitely increased were much less so than in the cases of leukemia above referred to. In a case of carcinoma of the breast the lesion consisted of hard, brawny, fibrous tissue in which one would expect little or no autolysis. In this case there was practically no increase in the products of nitrogenous metabolism, and only a moderate increase in the total acidity of the urine.

From the above it would appear that the changes in the urine as a result of the radiation of the pathological conditions above referred to are due in part at least to the products derived from the autolysis of the abnormal tissue under the influence of the radiation from radium. These results throw no light upon the nature of the constitutional symptoms which have been described resulting from the radiation of radium and of the X-rays. Only one of our cases in this series showed any systemic reaction because of radiation and in this instance the nitrogenous substances in the urine did not show as excessive increase as in the cases of leukemia which showed no general symptoms of toxemia[101].

Phagocytic Power of the White Blood Cells in Leukemic Blood

Not only is the physiological activity of the large numbers of premature white blood cells indicated by the increased oxygen requirement, as shown by Grafe[90], but the function of the leukocytes in leukemia is also shown by their capacity for phagocytosis.

In the blood of patients with myelogenous leukemia we have found that phagocytosis is less active the more the white cells depart from the morphological adult type; in the latter, however, phagocytosis is prompt and marked, and although the relative number of these cells may be less, the absolute number is markedly increased.

Achard, Ramond and Feuillie[102] believe that the phagocytic power of the leukocytes of the blood in myelogenous leukemia is more feeble than that of normal individuals. This is confirmed by Parvu[103] who thinks it due to deficient opsonins for on adding normal blood phagocytic power was shown by the mononuclear cells of the same leukemic blood. De Moralus in four cases of myelogenous leukemia found that the white cells showed enfeebled phagocytic and opsonic power, but that all the leucocytes possessed phagocytic power except the lymphocytes.

The work of Tschistovitch and Arinkine[104] confirms the observations above mentioned that (1) the phagocytic power in leukemia is always enfeebled, (2) the phagocytic power is especially marked in the polymorphonuclear neutrophils which are also the phagocytes par excellence of normal blood, (3) the unripe forms of leukocytes, which one finds in great quantity in the blood of leukemias, possess a feeble phagocytic power or they may lack it entirely. This power belongs to some forms of mononuclears, probably to those from which the polymorphonuclear neutrophils are derived. Therefore, it appears only at a certain stage of the development of leukocytes, (4) that white cells of leukemias which resemble one another from the point of view of their differential count may present very sharp dissimilarities in regard to their phagocytic power.

These phagocytic properties of leukemic blood may explain the changes caused in the white cell counts by certain infections and also the lack of resistance to infections in certain stages of leukemia.

Complement Content of Serum and Plasma of Leukemic Blood

The view has been advanced that complement is formed by the white cells. Gurd[105] believes that complement occurs in the circulating plasma as complementogen and is rendered active as a result of the liberation of some substance, probably similar to thrombokinase, which is produced chiefly by the white blood cells. As the white cells in leukemia are in great part abnormal morphologically it may be argued that their function is likewise perverted.

The blood in leukemia shows such striking numerical and morphological changes that it seems possible that alterations in the function of the cells or plasma might be detected by examining certain biological properties of the serum. A study was made by Ordway and Kellert[106] on the hemolytic property of the blood serum and citrated plasma with particular reference to its complement content. It was thought that if the complement is produced by the activity of or the disintegration of white blood cells it might be correspondingly increased in cases of leukemia.

In this series there were five cases of leukemia, three myelogenous and two lymphatic; one of the myelogenous cases gave no hemolysis in amounts from 0.01 to one cubic centimeter. Of the two remaining cases of myelogenous leukemia one with white count averaging 585,936 per cubic millimeter had a titer of 0.2 cubic centimeter and one case having a white count of 608,800 had a titer of 0.1 cubic centimeter. Both cases of lymphatic leukemia one acute and rapidly fatal and the other of chronic type with white count averaging 234,000 also had a titer of 0.1 cubic centimeter. From this it seems evident that the hemolytic complement of the serum in lymphatic and myelogenous leukemia is not increased (Ordway and Kellert[106]).

Production of Antiserum, Leukolytic for Leukemic White Blood Cells

It has been claimed that the action of the X-ray in reducing the number of the circulating white blood cells in leukemia is indirect and not due to the direct action of the physical agent upon the abnormal cells. This indirect action is believed to be due to the fact that the blood serum, as the result of radiation, develops leukolytic properties[107]. We have been able to produce an active leukolytic serum by repeatedly injecting into a rabbit white blood cells from cases of myelogenous leukemia.

Production of Bacterial Antibodies in Leukemic Blood

Investigations of the serum in cases of leukemia in reference to the production of antibodies have been made by several observers. Moreschi[108] in twelve cases of leukemia by means of the injection of typhoid vaccine was able to detect very little or no formation of agglutinins nor was there local or general reaction to the vaccine. From these observations he believed that in leukemia the pyogenic and antigenic action of the typhoid bacillus is either inhibited or it may be inferior to that of normal individuals. Hoke[109] showed that leukemic blood contains products which destroy bacteria and Stenström[110] found that when leukocytes and bacteria were injected into rabbits there was less antibody production. Rotky[111] using a harmless vibrio cultivated from water found in eight control cases having various diseases that there was no local or general reaction but that agglutinins were produced. In two cases of leukemia, one myelogenous and one lymphatic, he found no agglutinins formed and believes that the bone marrow was unable to produce agglutinins or that the excess of leukocytes broke down the antigen so that it did not stimulate antibody formation. It is because of this he thinks that mild infections may prove so severe to leukemic patients.

Presence of a Leukotoxic Factor in Leukemic Blood

Packard and Ottenberg[112] believe that there is a leukotoxic factor in lymphatic leukemia. They draw a close analogy between the aleukemic or sublymphemic stage of leukemia and aplastic anemia in both of which there is a great diminution of the granular leukocytes in the circulation. They consider the toxic factor similar in certain respects to the action of benzol which was used by Selling[113] experimentally to produce a similar destruction of granular leukocytes.

These authors think that there is in leukemia both an overproduction and also an accelerated destruction of leukocytes, and that the number of white cells in the circulation at any one time depends upon which of these two processes predominate. In a case of chronic lymphatic leukemia a large transfusion was done and the granular leukocytes added by the donor's blood entirely disappeared from the circulation twenty-four hours after the transfusion. They conclude that these leukocytes were either destroyed, or were held in the internal organs. The transfused red blood cells were not rapidly destroyed. Hence the destruction of leukocytes was not due to total blood destruction, but to an hypothetical leukotoxic factor in the blood of the leukemic patient. This factor, if its existence is confirmed experimentally, might be a similar antibody occurring naturally in vivo analogous to the leukolytic antibody which we produced experimentally in rabbits and proved to be strongly leukolytic in vitro.

Presence of Ferments in Leukemic Blood—Proteolytic: Oxidizing

It has long been recognized that the leukocytes from the blood of cases of myelogenous leukemia contained a ferment which is capable of digesting fibrin. Both the polymorphonuclear leukocytes and myelocytes contain enzymes that are capable of digesting blood serum. This enzymotic action has been found in the cells from the blood of cases of myelogeneous leukemia by Jochmann and Müller[114] and by others, but these investigators have failed to demonstrate that lymphocytes either from cases of lymphatic leukemia or lymph nodes from cases of pseudoleukemia possess any such action.

In view of the discussion as to the origin of the large lymphocytes in so-called acute lymphatic leukemia and their relation to the granular myelocytes on the one hand and the non-granular lymphocytes on the other the conclusions of Longcope and Donhauser[115] are of interest. These authors found that the leukocytes of the blood of normal individuals and of patients showing a marked polymorphonuclear leukocytosis contain enzymes capable of digesting coagulated blood serum in neutral, alkaline, or acid solutions. The cells in pus that is composed chiefly of polymorphonuclear leukocytes and the leukocytes of the blood in myelogenous leukemia contain similar proteolytic enzymes which act best when the reaction is alkaline. The leukocytes of the blood and of the enlarged lymph nodes from a case of large cell acute lymphatic leukemia contain proteolytic enzymes that act qualitatively in much the same way as the leukocytes of pus and as the white corpuscles of the blood in myelogenous leukemia. These large lymphocytes in so-called acute lymphatic leukemia can be differentiated biologically from the small lymphocytes in chronic lymphatic leukemia which possess no proteolytic enzymes and from the large endothelioid cells of the hyperplastic lymph glands which are proteolytic only in the presence of acid. These results seem to show that the large cells of the so-called acute lymphatic leukemia are not true lymphocytes but are related to the granular myelocytes and should probably be considered as the forerunners to these cells. This view is further strengthened by the way these cells react in studies on phagocytosis and to staining methods for the demonstration of the so-called peroxydase or oxidizing ferment.

The oxidizing ferments of polymorphonuclear leukocytes and myelocytes were first recognized through observations that pus and leukemic blood contain some substances capable of producing a color change in tincture of guaiac. The method developed by Winkler[116] for demonstrating the so-called oxydase or peroxydase substances consists of aqueous solutions of alphanapthol and of dimethyl para phenylene diamin. The oxidation of such a mixture results in the formation of indophenol. In smears of pus, blood and bone marrow Winkler found that this reagent brought about a deep violet coloration of the granules of certain cells and concluded that these granules had been stained by the dye synthesized through the activity of an oxidizing ferment or oxydase contained in them. He believed that all white blood cells contain oxydase, although he admitted a quantitative difference in the amounts held by the myelocyte series and by lymphocytes. Brandenburg[117], however, maintained that the lymphocytes are devoid of oxidizing substances. This was confirmed by Meyer[118] and Schultze[119]. Brandenburg advocated the use of the Winkler reaction on blood smears as a means of differentiation of leukemia and emphasized its value, particularly in the differentiation of immature myelocytes, sometimes encountered as the predominating form in acute myelogenous leukemia, from the large cells of acute lymphatic leukemia. The method of Winkler, however, has not proved entirely satisfactory. The solutions rapidly deteriorate, even when carefully protected from air and moisture. The compound is very unstable in the aqueous solution used for the reaction and the stained preparations are not permanent, but usually fade out in the course of a few hours or days. Evans gives the life of the stain as ten minutes. Graham[15] modified the Winkler method of treatment of blood smears and tissues with an alphanapthol solution containing small amounts of hydrogen peroxid. Blood smears treated with the alphanaphthol solution followed by pyronin and methylene blue present a picture much like that given by the Romanowsky stains. The granules of polymorphonuclear leukocytes and myelocytes are, however, much more definitely indicated. In frozen sections stained with a mixture of alphanaphthol solution and pyronin and counterstained with hematoxylin the granule-bearing cells are sharply differentiated and the sections can be cleared and mounted in balsam. More recently Graham[120] has described a method in which benzidin is employed as a peroxydase reagent for blood smears and tissues. This stain is permanent, easily prepared, and it may be counterstained by any of the so-called polychrome stains such as Wright's stain or a modification described by McJunken[121]. As a result of these improvements in technique the evidence seems to indicate that there is an enzyme of the so-called peroxydase group. The presence of this body in the leukocytes of the myelocytic series and its absence in the lymphocytic series is another biological argument for the fundamental dissimilarity of these two cell groups.

Theories of Causation and Relationship to Other Pathological Conditions

The cause of leukemia is unknown. Certain microorganisms have been described as the causal agent of or found associated with this disease. The evidence, however, that such organisms cause leukemia is far from conclusive.

It has also been claimed that certain infections are related to the development of leukemia, notably acute and chronic pyogenic suppuration, tuberculosis and syphilis. The relation of the leukemias to various pathological conditions frequently classed as tumors, notably Hodgkin's disease, chloroma and the lymphomata, is very close. Indeed, certain pathologists consider that the leukemias are new growths of the blood forming organs, the cells of which undergoing rapid proliferation invade and multiply in the circulating blood.

Heredity, race, age, sex, trauma, altitude, mental and physical states are claimed by some to be factors in the development of leukemia, but of this there is no conclusive evidence. The study of leukemia and allied conditions in mice, fowl and apes has already given suggestions as to the nature and transmissibility of leukemia and the continuation of such investigations should yield important results.

There is no valid evidence that leukemia is caused by the various microbodies described in leukemic blood or tissues[122, 123, 124, 125], nor has any agent been proved to be the cause of this condition.

The likeness of leukemia to various infections is particularly marked in the more acute cases[126, 127, 128, 129, 130, 131, 132] and in the acute terminations of chronic types of the disease. In the chronic disease also the irregularly elevated temperature, the anemia and the prostration suggest a more chronic and less virulent infection. Various bacteria have been described as occurring in the blood or tissues of leukemic patients; streptococci[77, 133, 134, 135, 136], tubercle bacilli[153, 155, 156], cornyne bacterium[137, 138, 139, 140], staphylococci[7] and mixed organisms[141].

In an analysis of 1,457 cases of leukemia of all varieties Ward[24] concludes that the evidence does not favor the infectious nature of leukemia for (1) there is a congenital form of leukemia which occurs in children whose parents are not leukemic, (2) leukemic parents have never been known to transmit the disease to the new-born child, (3) instances in which actual infection of one person by another might seem to have occurred are very few, (4) leukemia differs from infectious diseases in having a marked preference for a particular sex and age.

On the other hand, such high leukocyte counts as those noted in certain cases of typhoid fever[7], pneumonia and other ordinary infections[5, 39, 142, 143] and the leukemic blood changes following upon injury, fracture and definite bone infection[7, 35, 144] are regarded by Wilber[77] as more than suggestive of the infectious nature of leukemia.

Recovery (reported by Cabot[5], Jackson and Smith[145], and Türk[146]) of certain patients with marked lymphocytosis, regarded in certain instances by the writers as leukemia, leaves one in doubt of the real identity of such conditions, for we have learned that in some typical cases of the disease leukemia the entire clinical course of the disease, the blood picture, and the autopsy findings, with particular reference to the bone marrow and such special staining methods as the improved oxydase staining technique (Graham) are necessary before the diagnosis of leukemia can be accepted as correct.

It is well known that various infectious agents may give rise to an unusually marked leukocytic response evidenced in the blood[147]. Certain intestinal infections[148, 149] and tonsillar foci[150] are reported to have caused marked changes in the white cells of the blood. Dohrer and Pappenheim[151] have described a special tendency to leukemia on the part of the blood producing tissues which they term a "leukemoid reaction of the blood during sepsis." Organisms of low virulence localizing in the bone marrow following fracture due to gun shot wounds are reported to have caused leukemic blood pictures[35, 152, 153].

Because of the varied responses of the bone forming organs to recognized infections, Wilber[77] urges the need of etiologic instead of purely morphologic study of leukemia. He considers the artificial borders broken down between leukemia and leukemic changes in the blood in the presence of established infections, and emphasizes the variability in the blood findings in different patients, and at different observations in the same patient.

He regards the leukemic process as the result of the infection, or a secondary toxicosis of the bone marrow, spleen and lymphatic structures. The abnormal blood cell production may be due to some unknown organism, or to several different organisms when the physiological conditions of the hematopoietic organs are favorable to such a response.

Not only the acute and chronic pyogenic infections causing suppuration have been regarded as related to the development of leukemia, but also organisms producing proliferative changes, notably the tubercle bacillus and the diphtheroid organism known as cornyne bacterium. Cases of tuberculosis are recorded in which the blood picture resembled that of leukemia[154, 155, 156]. Nanta[129] has reported such a case and has collected the literature and made observations on tuberculosis as related to myelogenous leukemia or to hyperplasia of the myeloid system. Such observations, however, are apparently of only theoretical interest as the actual coexistence of tuberculosis and leukemia is rare and there is no valid evidence of a causal relationship.

A few cases are reported in which a strongly positive Wassermann reaction has occurred in a leukemic patient. Two such cases have recently come to our attention.

Hodgkin's disease, sometimes referred to as malignant granuloma, though, as yet of unknown origin, seems to be related to the chronic infectious granulomata, notably tuberculosis on the one hand and to leukemia on the other. It is also regarded by numerous pathologists as a variety of that group of tumors known as lymphomata, and has even been classified by Mallory[157] as a scirrhous lymphoblastoma. As the condition known as Hodgkin's disease has been confused clinically with certain forms of cervical and abdominal tuberculosis so histologically and bacteriologically the two conditions have led to misunderstanding, for Hodgkin's disease and tuberculosis may be coexistent in the same gland and one may antedate the other. The finding of the so-called Much's granules in the tissue of such glands has increased the difficulty. Fraenkel[158] believes that this organism is closely related to, if not identical with, the tubercle bacillus. The question has been raised whether these granules were really tubercle bacilli in a specially resistant form or another variety of organism. It has been shown by numerous investigators by means of cultures and smears that these granules are really diphtheroid bacilli called by Negri and Mieremet[164] cornyne bacteria.

It has been argued [159, 160, 161, 162, 163, 164] that this organism is the cause of Hodgkin's disease. Although in certain respects the organism resembles the granular forms of tubercle bacillus it is not acid fast and does not give rise to tuberculous lesions in laboratory animals. Bunting and Yates report the production of so-called Hodgkin's blood picture in laboratory animals inoculated with the living organism and in one normal individual inoculated with the dead organism or vaccine of the diphtheroid bacillus. Although Billings and Rosenow[165] isolated from the lymph glands a diphtheroid bacillus from twelve cases of Hodgkin's disease in only three instances was the culture pure. In the others staphylococcus was also present.

In 1916 Billings, in a discussion of the work of Bunting and Yates[140], stated that although the diphtheroid bacillus had been recovered from the lymph glands in over forty cases of Hodgkin's disease and other lymphatic diseases in all except two instances, the same organism had also been found in goiters, joints, tuberculous glands, etc. He, therefore, concluded that the cornyne bacterium is a parasitic organism accidentally present in pathological tissue and does not have any etiological relationship to lymphatic diseases. At certain times if the blood picture is carefully followed in cases of Hodgkin's disease there may be shown a markedly increased number of leukocytes in the peripheral blood reaching from 50,000 to 60,000 and the condition may closely simulate leukemia.

In view of what has been said it was not surprising that certain writers[137, 139, 140] reported the finding of diptheroid bacilli in the lymph glands from cases of lymphatic leukemia, pseudoleukemia and chloroma. Simon and Judd[138] also isolated diphtheroid organisms from lymph glands of a case of acute leukemia but make no claim to its etiology.

It is obvious that opinions concerning the etiology of leukemia vary greatly. Notwithstanding the similarity and possible relation to the infections, above described, the condition is regarded by many[157, 166] as closely related to the tumors, the cells of which are those of the blood making organs. In the more acute cases the more primitive cells of the lymphocytic or myelocytic series predominate. In some instances the greatly increased blood forming cells are confined to the blood vessels and the hematopoietic organs. In other cases there is a tendency for a greater or less invasion of the various tissues by the blood forming elements. In such instances the condition is closely analogous, if not identical, to the malignant tumors.

Sarcoma[167, 168], myeloma and lymphosarcoma have been reported as existing with a blood picture like leukemia. Indeed, it is now agreed that the so-called chloroma, formerly described as a malignant tumor, is a condition in which the primitive blood forming cells of the myelocytic series occur in definite tumor-like nodules scattered throughout the various tissues and organs. In other words, chloroma is regarded as a variety of leukemia.

The leukemic and aleukemic character of various lymphomata is seen not only in the human being but in fowl. Tyzzer and Ordway[19] reported a series of tumors in the common fowl among which was a case of lymphoma associated with lymphatic leukemia and five cases of lymphoma without invasion of the blood stream. The main distinction between aleukemic lymphoma and lymphoma with leukemia is that in the former the tumor is extravascular while in the latter it is largely intravascular; in certain cases the tumor is both extravascular and intravascular in its growth. The cells of these lymphomata in the fowl most frequently resemble those of the germinative centers of lymph follicles. Such tumors, when inoculated, readily grow in the same individual but with considerable difficulty when inoculated into other hens. They apparently demand peculiar conditions which are more suitable in the individual in which they arise. Such tumors present the properties of malignancy, that is, unlimited growth, infiltration of normal tissue and metastasis. The leukemic or aleukemic tumors in fowl may occur as a definite primary growth either with or without secondary nodules or the condition may be so disseminated that the site of origin cannot be determined. The peculiar cellular reaction of fowls, however, makes it difficult to apply directly the results obtained to the subject of tumors in mammals. Whether the characteristic growth of cells in aleukemic and leukemic leukemia, in both lower animals and man, is the result of cell stimulus from within, as in most forms of true tumor growth, or is due to the introduction of a stimulus from without, a filterable substance, ultramicroscopic virus, or a physical or chemical irritant, is at present in doubt. It is possible that several etiological factors are involved and that these upset the normal balance of blood cell production and blood cell destruction and hence lead to leukemic, subleukemic and aleukemic phases or types of the disease.

THERAPEUTIC MEASURES

The treatment of leukemia was largely empirical or symptomatic measures were adopted for combating the associated anemia until it was found that certain agents had a more or less specific effect in reducing the greatly increased number of white blood cells.

The measures directed toward the associated anemia commonly used are arsenic in the form of Fowler's solution, cacodylate of iron, and more recently arsphenamin. The injection of whole, defibrinated, or citrated blood, and the administration of iron in various forms and red bone marrow have also been advocated. Metals in the colloidal state are said to have caused improvement.

Of the measures directed toward the destruction of the abnormally increased white blood cells the X-ray, benzol, radium, mesothorium, thorium-x, have been used to induce remissions in the chronic type of the disease. The acute form is apparently not influenced by any treatment. The treatment directed toward reducing the number of abnormal white blood corpuscles above referred to offers the greatest chance for improvement. The most commonly used is the X-ray, next benzol, but with proper technique radium seems to give the best results.

Symptomatic Treatment

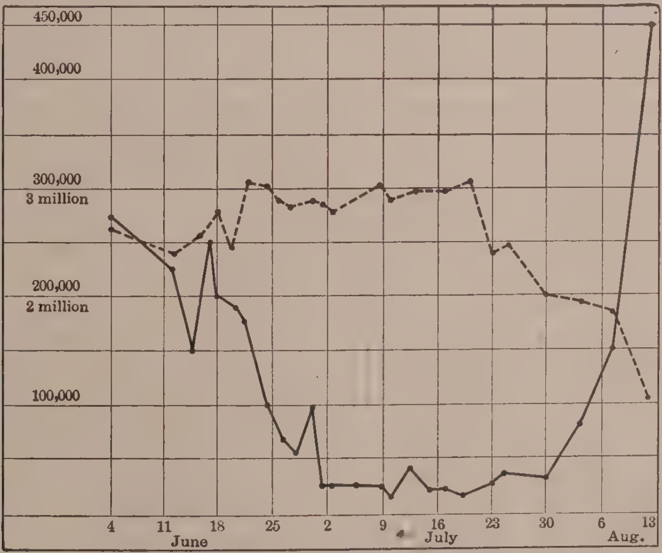
For symptomatic treatment of the associated anemia in cases of leukemia it has long been the custom to give some form of arsenic such as Fowler's solution in increasing doses to the physiological effect, or sodium cacodylate, and more recently arsphenamin has been employed. Iron in various forms, notably freshly made Blaud's pills, in five or ten grain doses (0.3 to 0.6 gm) three times a day is commonly used for the anemia associated with leukemia.

Cawadias and Monphrrato[169] report a case of lymphatic leukemia in which the white count was reduced from 103,000 to 62,000 after three intramuscular injections of 5 c.c. each of colloidal gold and another experiment in which the white count before injection was 40,000. Eight hours after the injection of 3 c.c. of colloidal sulphur it became 28,000. Twenty-four hours after injection it was reduced to 19,000. They also report observations on a case of myelogenous leukemia in which the white count two hours after the injection of colloidal gold was reduced from 630,000 to 544,000 and twenty-four hours later to 512,000. They conclude that colloidal metal acts like benzol and X-ray. Colloidal metals, however, have not been actually used therapeutically in leukemia.

Because of the fact that the white count in leukemia is frequently lowered by intercurrent infection and in certain instances a remission in the disease is induced, Larrabee[170] used the toxin of a streptococcus and bacillus prodigiosus, developed by Coley for the treatment of sarcoma, and succeeded in reducing the white blood cells in leukemia but his treatment apparently only slightly modified the course of the disease.

Benzol Treatment

The use of benzol in the treatment of leukemia rests upon the observations of Selling[171] that benzol has a leucotoxic action. Barker observed three cases of grave aplastic anemia with striking leukopenia apparently caused by the exposure of the patient to crude benzol; this laid the foundation for the experimental work of Selling above referred to. Koranyi[172] reported a series of cases of leukemia treated with benzol with favorable results. Kiralyfi[173] reported seven cases with good results. Billings[174] added five cases. In the year 1913 he showed that benzol might act like a two edged sword producing, on the one hand, favorable results and, on the other, annoying and even serious disturbances. Wachtel stopped the use of benzol in two cases because of albuminuria. Klemperer and Hirschfeld[175] thought that benzol was dangerous because it caused serious injury in animals and that acute termination of leukemia was coincident with or subsequent to the use of benzol. Graham[82] has reported such a case. (Fig. 5.)



Solid line, white cell-count; broken line, red cell-count.
Benzol 15 minims, gradually increasing to 45 minims, daily from June 7 to July 30.

FIG. 5.—Chart illustrating acute myeloblastic termination in a case of myelogenous leukemia treated by benzol. Taken from article by Graham, *Jour. Amer. Med. Assoc.*, 1915.

Türk[176] called attention to the experimental work of Pappenheim who showed that 4 c.c. of benzol caused rapid death in a rabbit weighing 1,200 to 1,500 grams and 3 c.c. caused severe cachexia and death in three weeks. In these animals he found constantly severe damage to the parenchyma of the liver and especially the kidneys. Schmidt believes that the results of benzol are best in the myelogenous form of leukemia and occasionally in the lymphatic type but in the latter considers the X-ray preferable. He considers it advisable to stop treatment when the white count has been reduced to 25,000.

Billings[174] concludes that following the therapeutic use of benzol there is a tendency at first to a rise in the leukocyte count but that within ten to fourteen days after the patient has been given the drug there is a rapid fall in the number of leukocytes in most cases, and that there is a corresponding rapid diminution in the size of the spleen and liver, more rapid than when the treatment is by X-ray alone. As a rule there is also an incréase in the number of red blood cells and hemoglobin. Billings[174] believes that in the lymphoid type of leukemia the drug acts more rapidly than in the myelogenous form with a very rapid fall in the number of white cells but that there is not the same improvement in the red blood cells and hemoglobin. Stained specimens of blood showed very early marked degeneration of the leukocytes which undergo various forms of necrobiosis.

The patients in the series reported by Billings showed improvement as the result of treatment by benzol but all his cases were also treated by the X-ray at one time or another. Benzol has a powerful effect upon the medulla of the bones. It seems to render the leukoblastic marrow less active and in the myelogenous type to make erythroblastic tissue hyperplastic. The poisonous effect of benzol upon the bone marrow indicates that this drug must be given very carefully or aplastic anemia may result. Because of this dangerous nature of the drug and the untoward symptoms above referred to each individual case should be tested out carefully.

In 1913 Koranyi[177] reported favorable results from the action of benzol in the majority of the eighty cases reported in the literature. He emphasized certain contraindications for benzol and particularly the fact that high doses may have a destructive effect upon the red blood cells, whereas the proper dose stimulates red cell formation, the number mounting up to 6,000,000. The most serious danger of benzol is the overhanging of the action after the drug has been stopped; also hemorrhages in the skin and mucous membrane, high grade anemia, fever and almost complete disappearance of the white cells from the blood are signs of approaching death. Rolleston[178] reports temporary benefit from benzol treatment in a case of chronic lymphoid leukemia but believes this treatment should be avoided when the case is very acute with fever; also in nervous subjects particularly in cases with a high degree of leukemic retinitis.

In Graham's case[82] of chronic myelogenous leukemia for eight weeks following the administration of benzol there was a marked reduction in the number of white cells, a moderate increase in the number of red cells. Towards the end of the treatment, however, there was a rapid reduction of the red cells and a remarkable increase in the number of white cells, patient dying with an acute leukemia termination. See chart (Fig. 5). As previously noted, however, such acute myeloblastic termination may occur with various forms of treatment and without treatment in cases of chronic leukemia.

The methods of administering benzol in the treatment of leukemia have now become almost uniform. Capsules, in certain instances coated with salol, containing 0.5 gram of benzol are given with equal parts of olive oil to diminish the irritating local effect, such as eructations of gas, tasting and smelling of the benzol, burning in the stomach, and dizziness. Two such capsules are given at first, increasing until ten, that is five grams, a day are administered. Billings recommends four grams daily and Koranyi begins with three grams and increases to four or five grams daily. They should be taken immediately after meals and never during meals and it is important that patients should be kept in the hospital during such treatment. It may take ten days to three weeks before the effect upon the blood is observed. It is customary to stop administration when the white count in leukemia has been reduced to 20,000. Boardman[179] states that sixteen out of one hundred cases fail to show improvement and that another eight cases, although reacting favorably at first, died during or soon after the discontinuance of treatment. Also certain toxic effects have been reported such as gastrointestinal disturbances, headaches, dizziness, skin eruptions, bronchial and kidney irritation and hemorrhages. Marked leukopenia with increasing anemia and death may occur.

From the above we may conclude that benzol if administered carefully is of definite value in a considerable percentage of cases of chronic leukemia. Most writers believe that the results are improved if used in conjunction with the X-ray. The authors believe, however, that the proper use of X-ray and radium gives better results in the treatment of leukemia than are secured by the administration of benzol.

Recently Haughwout and Asuzano[180] while using benzyl benzoate for the relief from abdominal pain and distension in a case of lymphatic leukemia confirmed the statement of Macht[181] that the administration of benzyl benzoate by mouth was not followed by any untoward or disagreeable symptoms even in patients who are in poor health. Ten drops of a 20 per cent. alcoholic solution of benzyl benzoate in water were given three times a day after meals. There was a marked improvement in the patient's general condition, temporary reduction in the white count and moderate diminution in the size of the spleen and liver. No positive conclusions can be drawn from the treatment of this case but it appears to be free from evil tendencies shown by the related compounds and it can be administered indefinitely. The treating of patients of leukemia in earlier stages of the disease and using larger doses of the drug, benzyl benzoate, is suggested by the authors.

Roentgen Ray Treatment

Since 1904 Beclere[182] has treated 110 cases of leukemia by means of the Roentgen ray, 12 of the lymphatic type, 93 of the myelogenous and 5 of acute leukemia. A large proportion of the cases showed at least temporary improvement. There was first a return of strength, diminution in the size of the spleen and glands, disappearance of insomnia, return of appetite, increase of weight and improvement in the color of the skin. The blood picture returned nearly to normal. Eventually, however, the treatment had no action on the progress of the disease and the patients died of cachexia, thrombosis or complications of the heart, lungs, kidneys, or intestines. Beclere directed all his efforts towards the enlarged spleen in the myelogenous type of the disease and as this diminished in volume all other symptoms improved. This has also been the experience of the writers in treating cases of myelogenous leukemia by means of radium. Beclere now believes that the results were due to the fact that in the greatly enlarged spleen the radiation was affecting a considerable mass of blood and that the treatment was, unfortunately, only symptomatic. He never obtained results so striking and so rapid on X-raying the bone marrow. All cases of myelogenous leukemia favorably reacted at first. The fall in the white count was rapid. In one or two months there was great improvement in the general condition and the spleen diminished in volume almost to normal. The fever fell, eye, stomach and intestinal symptoms and even hemorrhage and albuminuria disappeared. Weight increased and in women catamenial periods became normal and regular. Beclere describes this remarkable temporary improvement as follows: "Il y a dont une veritable resurrection et il s'agit la une chose constante." Yet in spite of the great general improvement and the return of the blood to almost normal condition careful study always shows myelocytes one to every three hundred white cells. He regards this as the open door to a recurrence and proves that radiation is only symptomatic medication and not a cure. X-ray treatment also improves recurrences, sometimes again and again but finally becomes powerless. By following the blood closely Beclere has been able to keep leukemics in a state of health for from three to six years.

Pancoast[183] also believes that the results of X-ray treatment are still only palliative but may prolong life from a few months to six or even eight years. He advises application mainly and primarily against what he considers the primary focus of the disease, that is, the bone marrow, and leaves the raying of the spleen or glands to a later and safer time. He believes that the X-ray is better and safer than benzol and opposes the use of the two at the same time.

The technique for treating leukemia by the Roentgen ray has been very variable and this may account to a certain extent for the variations in the results obtained. Boardman[179] states that the X-ray has produced improvement in from twenty per cent. to fifty per cent. of the patients, that is, fifty per cent. to eighty per cent. of the cases are refractory. In most cases the long bones as well as the spleen have been radiated. In many instances, however, too little attention has been paid to the principles of cross fire and filtration (deep therapy). The principle of the so-called cross fire is important for the successful application of radium or X-rays to large growths or to deeply seated lesions. The method was first described by Domenici[184] and has since been elaborated by others, notably in the treatment of uterine fibroids by X-rays in the Freiburg clinic by Kroenig and Gauss. The aim is to concentrate as much of the action of the rays as possible in the deep-seated lesion with the least possible injury to the overlying skin. This may be accomplished by surface applications of X-ray to a large number of areas on the skin by all possible ports of entry, anteriorly, posteriorly and laterally, so that each area will not be exposed too long or too intensely. This might be the result in applying the radiation to a single area for the time necessary to produce the desired effect on the underlying lesion. By this cross fire method enormous doses, even 1,000 to 1,500 Kiemboeck units, may be applied to the deep lesion when not more than 200 could be safely put through one particular surface area. Pfahler uses from 4 to 40 surface areas and passes a full dose through each, making a total of from 80 to 800 units.

To produce any marked effect upon the deeper tissues it is necessary to use screens or filters to check the less penetrating rays which would otherwise be absorbed by the superficial tissues and cause marked destructive changes there before the less numerous and more penetrating rays could act on the deeper tissues. In order to obtain the most penetrating X-rays for this method of so-called deep Roentgen therapy, it is necessary to employ a hard tube of high degree of vacuum and an electrical apparatus of high voltage, penetration corresponding to 8 or 9 Benoist. The rays are not all of equal penetrability, and it has been found that they are more homogeneous when the softer have been filtered out by an aluminum screen 1 to 3 millimeters in thickness. Beclere did not repeat radiation over the same area before fifteen to twenty-one days and thus avoided all injury to the skin. Certain roentgenologists also use a heavy piece of leather.

Those who have had extensive personal experience with and opportunity for intensive study of leukemia recognize that there have been cases which did not respond to treatment by X-ray or benzol. Indeed, following the use of benzol serious, even fatal, results have been reported and toxic symptoms also may occur after the use of the X-ray. In certain instances benzol may cause a short period of temporary improvement followed by rapid fatal termination. Such termination also may occur with other forms of treatment or without treatment. With the more recent improvements in X-ray apparatus by Coolidge and his co-workers and by perfection in the technique of clinical application, it is probable that the number of cases which are refractory to X-ray will be considerably lessened.

Radium Treatment

Renon, Degrais and Tournemelle[185] reported a series of twelve cases of leukemia in which marked improvement resulted from the surface application of radium over the enlarged spleen. Eight of these had already been treated with Roentgen rays with no advantage, or only with temporary improvement. Pinch[186] of the Radium Institute of London also makes reference to a case of myelogenous leukemia in which the results of radium treatment were excellent. Von Noorden and Falta[187] did not obtain any favorable results in leukemia by the use of radium emanation, even by prolonged treatment in the emanatorium.

Treatment by thorium-x and mesothorium, both in the technique of application and in therapeutic results attained is very similar to that of radium. Indeed, these agents usually contain varying amounts of radium. Falta, Kriser and Zehner[188], however, produced remissions in leukemia by the injection of thorium-x. In the small series of cases reported by them the immediate results were good but the cases had only been followed a very short time so that they did not draw any conclusions regarding end results of this treatment. German investigators have reported conflicting results from treatment of leukemia by thorium-x.

Kaufmann[189] reports a case of lymphatic leukemia treated by thorium-x one and one-half years with very good results. Reduction of the white count, size of the spleen and liver, with improvement in the general condition and qualitative betterment in the blood picture. He gives a good bibliography of the cases treated and methods of use of thorium-x. Von Noorden[190] has clearly described the dosage, application and results of the treatment of leukemia by thorium-x. In general, the results and methods of treatment are almost identical to those of radium.

Technique of Radium Application.—When radium is used for the treatment screens or filters of lead 2 to 3 millimeters in thickness, of brass 1.2 millimeters or other heavy metals such as silver, gold, or platinum, allow the penetrating hard beta and gamma rays to pass and intercept the alpha and soft beta rays which would otherwise be absorbed and cause destructive changes in the superficial tissues. As the amount of the more penetrating rays is only a small proportion of the total activity, less than five per cent., it is necessary in deep therapy to make exposures correspondingly long.

The principles of cross fire as well as deep therapy are made use of in the treatment of leukemia by surface applications of radium. The technique of such radium therapy may be illustrated by the striking effect of radium when applied in the proper manner to the surface over the enlarged spleen in cases of myelogenous leukemia. For this the following details have been elaborated. The area of the enlarged spleen is carefully and plainly marked out with skin pencil or grease paint, the outline being obtained by percussion and palpation. The various landmarks, such as the costal margins, anterior superior spine and crest of the ilia, the symphysis pubis and the umbilicus are marked. The patient is photographed in an erect position in both front and side views. A series of small squares 3 cm. in diameter, when the radium applicator is 2 cm. in diameter, are marked over the area of the enlarged spleen. It is important not to have the successive application areas too near together or the skin between them will be burned by the double dose. The squares thus marked out are numbered serially. A swathe of thin cotton cloth is carefully fitted to the abdomen and the outline of the spleen, bony landmarks and small squares is traced upon it. This swathe must be smoothly and accurately fitted and kept in accurate position by means of the landmarks above mentioned, for it is left in place during each single series of treatments. The purpose of this swathe is to avoid the irritation of repeatedly applying and removing the adhesive plaster which holds the radium applicator in place, for it has been found that the area which is being or has been radiated is particularly sensitive to injury from the repeated application and removing of adhesive plaster. Indeed, such added irritation may induce vesiculation, or even superficial ulceration of the skin. Tracings of the areas and landmarks marked on the swathe are now made on tracing cloth which serves as a chart for guidance in the following series of treatments. This affords a convenient and accurate method of recording the changes in the size of the spleen and in avoiding injury to the overlying skin in the effort to give sufficient radiation to the underlying lesion. With the chart as a guide the radium applicator, screened with two or three millimeters of lead, fifteen to twenty thicknesses of filter paper and wrapped in gauze is now applied to each of the squares in the order indicated. Giffin[191] uses a biscuit-shaped block of wood devised by

Tucker, 1.25 cm. of wood, two mm. of lead, 1.25 cm. of wood bored to receive the tubes of radium and above this two mm. of lead and another 1.25 cm. of wood. The whole is held in position by means of a simple canvas belt. It is necessary also to add at least as much filtration and protection to the external side of the applicator for the patient may inadvertently rest the arm or leg on the applicator during sleep and a severe burn may thus result. The filter paper is applied to avoid the irritating effect of the secondary rays from the lead and the gauze adds to the comfort of the patient. If it is desired the applicator may be rendered even more comfortable by substituting twenty-five to thirty layers of gauze instead of the filter paper.

After from four to six weeks a second series of treatments is usually necessary, the interval between being determined by examinations of the blood and by the local condition of the skin. Care in not resuming the treatment too soon, or too intensively, will lessen the constitutional or toxic symptoms and prevent the development of grave anemia. If the details here described are followed, however, no effect will be produced upon the skin other than very faint pigmentation after several series of radium treatments. It is advisable to stop radium treatment when the white cells have fallen to 15,000 or 20,000 for with a definite leukopenia there seems to be more likelihood of the occurrence of a crisis with severe anemia and hemorrhage[192]. The size of the spleen and the bony landmarks should be marked out, a new swathe fitted and tracings made at each series.

Duration of Application and Amount of Radium Used.—When from fifty to one hundred milligrams of radium element or millicuries of radium emanation are employed evenly distributed over a surface applicator 2 x 2 cm. in diameter and the filtration and protection above mentioned are used, the radium may be left in each position from four to six hours, four hours if there are one hundred milligrams, six hours if there are fifty milligrams and if the filtration is three millimeters of lead. With this amount of radium and the above technique, it is possible for complete remission in leukemia to occur with three series of treatments. Amounts of radium, however, as small as twenty-five milligrams, even when this is in the form of a tube, have reduced the spleen to normal size and have caused the characteristic improvement in the blood and in the general condition of the patient, but the time required is longer and the series of applications more numerous. Renon, Degrais and Dreyfus[193] suggest thirty to thirty-three centigrams of sulphate of radium applied for twenty-four to forty-eight hours and distributed over a surface of five hundred to six hundred square centimeters.

In the writers' experience, however, it has not been necessary, or, indeed, seemed advisable, when radium is used as the therapeutic agent, to radiate the long bones. Surface applications of radium over the enlarged spleen in the manner above described produce most remarkable improvement with striking changes in the size of the spleen, the blood picture and the general condition of the patient. In the course of a few weeks, or in certain instances in three or four months, after radium treatment by surface application a spleen which filled almost the entire abdomen, extended well to the right of the median line and into the pelvis and caused marked pressure symptoms has been reduced to normal dimensions so that it is just palpable below the costal margin. The white cells in the blood may be reduced from 500,000 to 6,000, the immature forms being especially affected. The hemoglobin increases from sixty or less to ninety per cent. Red blood corpuscles may increase from 2,000,000 to 5,000,000. The abnormal blood cells, myeloblasts and myelocytes, disappear. Indeed, the blood picture returns almost to normal, although some variation in the size of the red cells may persist and there may be relative lymphocytosis. A pale, emaciated, anxious individual with bony framework, stooping shoulders and enormously enlarged abdomen usually loses the anxious expression, becomes plump, the abdomen returns to normal size, the color and strength improve so that the patient may feel entirely well. The pathological condition, however, sooner or later is apt to relapse and response is less prompt in subsequent series of radium treatments. Some of the patients treated with radium have been followed for a number of years and kept in good condition by the occasional repeating of radium treatments. Certain cases, however, similarly treated have died of intercurrent infection or have succumbed to the original disease.

Peabody[194] reports symptomatic improvement in all cases of myelogenous leukemia treated by radium under his observation. Of thirty cases of myelogenous leukemia treated by radium Giffin[195] reports a marked improvement in twenty-six and in thirteen of these the improvement was remarkable. Hemorrhage was checked after one or two series of radium treatments.

Striking changes are found in the urine of patients with myelogenous leukemia treated by radium. There is a marked increase in the total nitrogen, urea nitrogen and ammonia nitrogen. The uric acid is slightly increased. The total phosphates are increased remarkably. There is apparently no accumulation of uric acid in the blood at least when the kidneys are in normal condition. Because of this marked increase in the metabolism it seems advisable to have the patient on a purin-free diet during and following the series of radium treatments. The changes in the metabolism of patients treated by radium resemble in certain respects those resulting from treatment by X-ray.

Comparison of Total Number of White Cells and Red Cells and of the Per Cent. of Hemoglobin Before, During and Following Radium Treatment.— From April to June the white cells in a case under observation varied from about 300,000 to 450,000, the red cells from 3,800,000 to 3,600,000, and the hemoglobin remained about sixty per cent. During this time, therefore, the sodium cacodylate treatment, above referred to, produced no marked effect. From July to November the white cells increased to 500,000, the red cells for a few weeks gradually increased to 3,900,000 and then decreased markedly during August and September to 2,200,000 and the hemoglobin diminished to fifty per cent. During the early part of this period the X-ray was begun and later, because there was no apparent beneficial influence from the X-ray, it was combined with benzol treatment. Shortly after the use of benzol the marked reduction in the red cells and the hemoglobin above mentioned occurred while the number of white cells was not diminished. Because of this and from the fact that there were definite toxic symptoms (see above) benzol treatment was omitted and although X-ray was continued for a short time there was no apparent change in the white cells or hemoglobin. The first series of radium treatment was followed by a fall in the white cells from 495,000 to 159,000, a rise in the red cells from 2,790,000 to 3,620,000, and the hemoglobin from fifty per cent. to seventy-six per cent. After the second series of radium treatments the white cells fell to 74,000, the red cells and hemoglobin rose to 4,020,000 and eighty-one per cent. respectively. After the third series of radium treatments the white cells fell to 5,800, the hemoglobin rose to ninety per cent. and the red cells to 4,800,000. The blood, numerically, remained normal for somewhat over three months when there was a sudden, rapid increase in the size of the spleen, multiple hemorrhages in the skin and mucous membranes, and the white count rose to 24,600, and the red cells decreased to 3,770,000. The record of the number of red and white cells and the percentage of hemoglobin is shown in Fig. 6.

Comparison of the Relative and Absolute Number of White Blood Cells in Relation to Radium.—Blood smears made upon slides were stained by both Wright's and Giemsa's stain. In making the differential counts the following simplified classification was adopted for the purpose of clearness.

Myelocyte.—The term myelocyte was used to include typical myelocytes with characteristic granules. The larger, non-granular myeloblasts, many of which morphologically it is difficult to distinguish from the large mononuclear leukocytes and cells transitional between these two forms of premyelocytes, were included under the general term myelocytes. Neutrophilic, basophilic and eosinophilic myelocytes were not counted separately.

Polymorphonuclear leukocyte.—With the polymorphonuclear leukocytes were also included the immature forms, some with granules and occasionally bilobed nuclei, the so-called metamyelocytes.

Eosinophil.—Under the heading eosinophils slightly immature forms were considered.

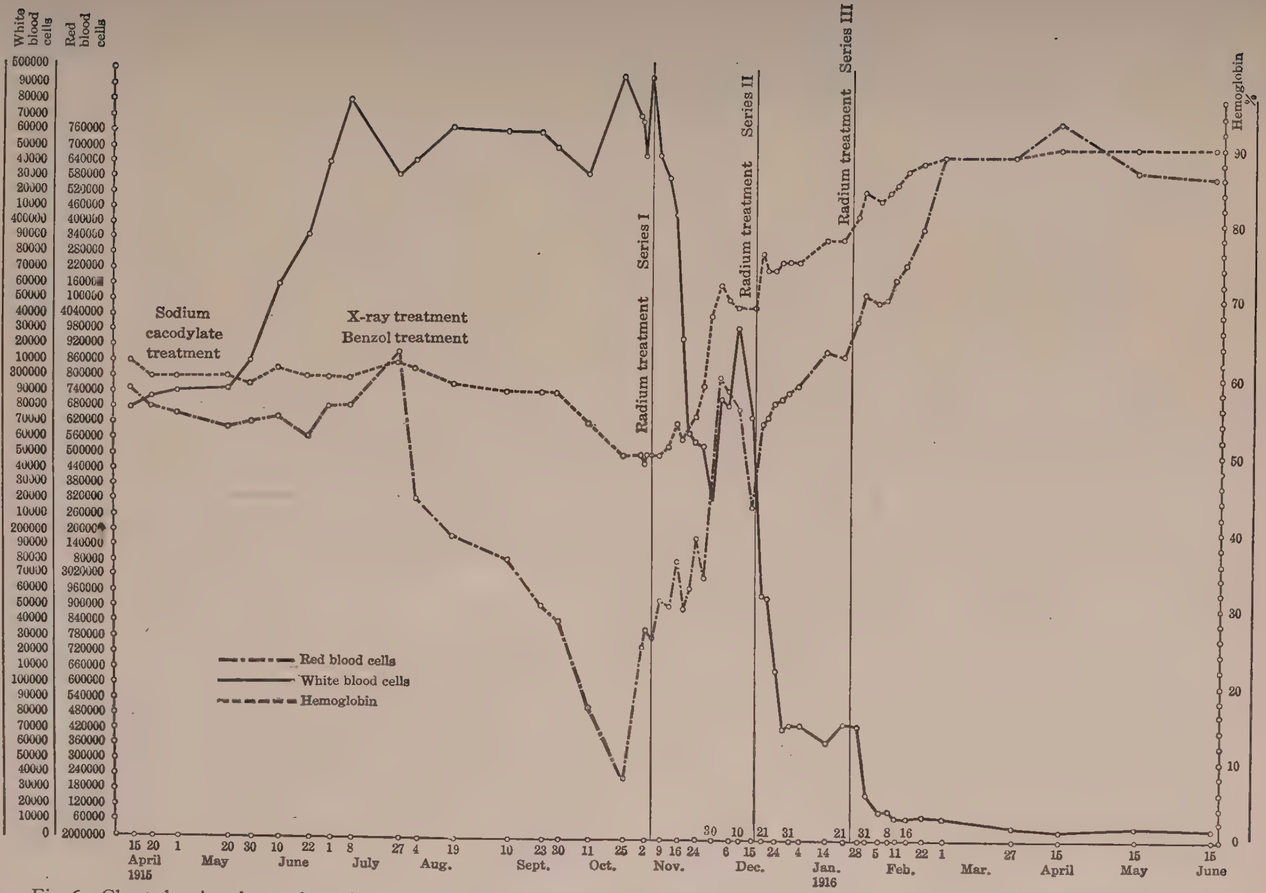


Fig. 6—Chart showing the total number of red and white cells and percentage of hemoglobin before, during and after radium treatment. Taken from article by Ordway, *Tr. Assoc. of Amer. Physicians*, 1916, XXXI, 177.

Lymphocyte.—No differentiation between large and small lymphocytes was made.

During the early months of the study of this case no attempt was made to differentiate morphologically between certain myeloblasts and large mononuclear leukocytes. Indeed, this would seem very difficult even with the aid of the oxydase reaction. In the latter part of the study, however, when all the myelocytes had disappeared following treatment, the term large mononuclear leukocyte was used. The so-called transitional and endothelial cells have been regarded as synonymous with large mononuclear leukocyte.

Mast Cell.—Only typical mast cells were included under this term.

Blast.—While making the differential counts an attempt was made to distinguish normoblasts, the intermediate forms and megaloblasts.

Following the radium treatment above described, the relative number of polymorphonuclear leukocytes increased from about 60 per cent. to 78 per cent. and then diminished to 50 per cent. Whereas, the absolute number fell from 299,475 to 2,917. The relative number of lymphocytes rose from 2.3 per cent. to 45.7 per cent. The absolute number of lymphocytes fell from 11,750 to 2,650. The relative number of myelocytes fell from 36 per cent. to zero and the absolute number of myelocytes fell from 178,200 to zero. There was little change in eosinophils, the relative number diminishing from 1.2 per cent. to 0.3 per cent. The increase in the large mononuclear leukocytes from zero to 3.1 per cent. is in part only apparent for the reasons above described. Mast cells increased from zero to 4.3 per cent. and later diminished to 0.6 per cent. The blasts, which were present as normoblasts, intermediate forms and megaloblasts, from 3 to 6 in counting between 500 and 600 cells, entirely disappeared. The records of the comparison of the relative and absolute number of white cells are shown in Fig. 7.

Morphological Appearance of Blood during Radium Treatment.—Blood smears at the beginning of radium treatment were typical of myelogenous leukemia showing large numbers of myeloblasts and myelocytes. The white count was 495,000, the polymorphonuclear leukocytes relative number 60.5 per cent., absolute number 299,475, myelocytes relative number was 36 per cent., absolute number 178,200.

During radium treatment the myelocytes diminished rapidly, the blood smears showing an apparent increase in polymorphonuclear leukocytes and a marked diminution in myelocytes. The total white count was 159,000, the relative number of polymorphonuclear leukocytes 65.3 per cent. and the absolute number was 103,827. Relative number of myelocytes was 28 per cent. and the absolute number 44,520. Following the three series of radium treatments the relative and absolute numbers of white and red cells and the per cent. of hemoglobin were normal and all abnormal white cells had

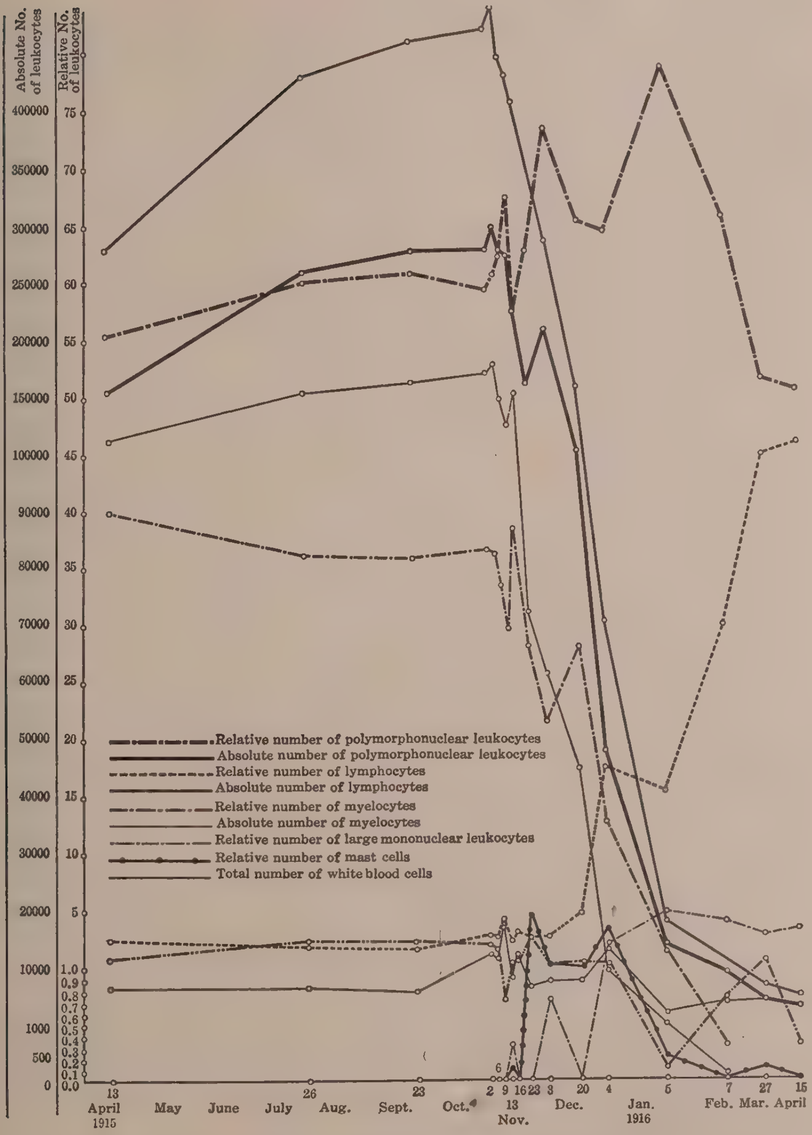


Fig 7.—Chart showing comparison of relative and absolute number of white blood cells before, during and after radium treatment. Taken from article by Ordway, *Tr. Assoc. of Amer. Physicians*, 1916, XXXI, 177.

disappeared. The red cells, however, even at the height of the patient's improvement continued to show considerable variation in size and shape.

Uric Acid in the Blood.—Chemical examination of the blood obtained on November 5, 1915, the day before the radium treatment, showed 3.78 milligrams per 100 c.c. of blood. Similar examination made of blood obtained November 27, 1915, three weeks after the treatment by radium had been commenced, showed 2.48 milligrams per 100 c.c. of blood. A third examination of blood obtained on March 3, 1916, about five weeks after radium treatment had been concluded, showed 3.5 milligrams of uric acid per 100 c.c. of blood. From the above it is evident that there is little change in the uric acid in the blood compared with the increase in the uric acid in the urine.

Summary of the Results of Radium Treatment.—Results similar to those above described in the treatment of leukemia have been reported by various observers who have used the X-ray for treatment, particularly when similar methods were used and the applications made over the enlarged spleen. In the majority of cases, however, the long bones have also been X-rayed. It is to be noted that in the surface applications of radium the results were obtained without radiating the long bones, in fact, in a case in which the long bones were radiated there was apparently an increase rather than a diminution in the white cells. It is also believed that the results are more prompt by the radium treatment than by the X-ray as usually employed and few cases have suffered from toxic symptoms such as nausea, vomiting, headache, dizziness, etc., although there is a marked increase in the endogenous purin metabolism. Reactions or constitutional symptoms have been observed and described by us, by Giffin, Peabody, and others. Such reactions may be due to too frequent or to intensive treatment. The latter may also cause profound and even fatal (Peabody)[194] anemia. Transfusion is indicated if the red cells fall below 2,500,000 (Giffin)[195]. On a purin-free diet, uric acid, urea, total nitrogen, phosphates and acidity of the urine are remarkably increased by radiation. Because of this it is advisable to have a careful examination of the urine before treatment is begun and to place the patient during and after treatment on a purin-free diet.

Sixty to one hundred milligrams of radium element or millicuries of emanation used by the technique above described would seem most satisfactory. Twenty-five milligrams of radium element, however, have produced similar results, although the number of applications was greater and the response much more gradual. In a case described in detail by us only three series of applications were necessary before the blood returned to normal. In other instances, with less perfected technique, six or more series have frequently been necessary.

Many of the cases which responded promptly to radium applications over the spleen had previously proved refractory to X-ray and benzol treatment. Although the results in the radium treatment of leukemia are most striking in the chronic myelogenous variety in certain cases of lymphatic leukemia the effects are almost equally as good. In the acute fulminating leukemias radium treatment is of no value. In some cases of chronic myelogenous leukemia, however, even when the general condition is very poor at the start there may be marked temporary improvement. It must be understood, however, that the results should be regarded at the present time merely in the light of palliation and not as a cure. It is hoped, however, that future research will at least increase the duration of these remissions. It has been suggested that the spleen be removed during the period of most marked improvement at the height of a remission when the spleen is of normal size and the general condition of the patient excellent.

Although radium treatment must not be considered at the present time as curative, from the results obtained it is the best form of treatment now at our disposal. The remissions last from months to years. In the case above detailed there was a remission of from six to eight months during which the patient was entirely free from symptoms of the disease. In other instances remissions have lasted from two to three years, although there is always a tendency for the disease to relapse and each recurrence responds less promptly and less completely to radium treatment. During the remissions patients may feel entirely well and assume the usual duties connected with their work and social affairs. They are, however, very susceptible to intercurrent infections. A case observed by us of fatal pneumonia occurred at the height of the improvement in the remission. Rapid recurrence and death by small gradual or massive hemorrhages or from weakness may occur after benzol or X-ray treatment and also, as in the case above described, after a remission produced by radium. Indeed, such rapid termination is common in untreated cases.

Authors' Conclusions Concerning Value of Radium Treatment.—1. Surface applications of radium in leukemia produce striking, indeed remarkable, improvement in (a) the blood picture which becomes almost normal, (b) in the size of the spleen and glands which are reduced almost to normal, (c) in the general condition of the patient who from an emaciated and weak condition may become plump and strong. 2. The duration of remission is variable; it may last from months to years. 3. The results of radium treatment are not regarded as curative. It is believed to be, however, the safest, as well as the promptest palliative measure in cases of chronic leukemia whether refractory or not to benzol or X-ray treatment. From the results of radium therapy in leukemia it is believed to be the best form of treatment now at our disposal.

Splenectomy Following Radium Treatment for Myelogenous Leukemia.—Although the results of splenectomy in leukemia have been almost universally fatal when undertaken while the spleen was enormously enlarged and the general condition of the patient was very poor, we suggested that when the spleen was reduced to normal size and the general condition of the patient was excellent following radium treatment, splenectomy at this time might prevent a relapse.

Giffin[195] reports results of splenectomy at the Mayo Clinic following radium treatment for myelocytic leukemia. In eighteen cases with preliminary radiation which had reduced the size of the spleen and the white count and improved the general condition one patient died, giving an operative mortality of five per cent., while mortality without radium treatment had previously been eighty-six per cent. or higher. Ten of the patients who were operated upon were living and in good condition nine months to a year and seven months after the operation. Yet the disease may recur. Of seven patients operated upon within six months of the onset of the disease six patients were alive at the time of this report. It is believed that in certain chronic types of myelogenous leukemia with fibrous spleen and a relatively low white count splenectomy may be justified for the comfort of the patient, but there is no evidence that the disease is altered in any definite way by splenectomy for recurrences are not prevented. The results of radium treatment were so good temporarily that it led to the inference that possibly malfunction of the spleen might be an important factor in the production and continuance of leukemia, for these results, remarkable temporarily, have been secured by direct radiation over the enlarged spleen. The results of splenectomy as reported by Giffin[195], however, do not justify this supposition.

UNUSUAL FORMS OF LEUKEMIA AND RELATED CONDITIONS

Atypical Leukemia

In the conception of leukemia presented there is no need of designating a particular case of leukemia as atypical. Formerly one heard of so-called mixed leukemia and leukanemia, but every case of true leukemia will show histological evidence of a predominating hyperplasia of either the lymphoid or the myeloid series of cells. Certain variations in the aggressive character of the growth occur, but there is no sharp definition of this and there are found all grades of proliferation from simple hyperplasia to massive tumor nodules. When brought together these cases are seen to represent a long series with connecting links of longer or shorter length. Were every case subjected to post-mortem examination and careful histological study, there would be many fewer instances of atypical leukemia reported. During life there may be confusing variations in the blood picture in some cases and we may properly speak of an atypical blood picture in leukemia, that is, one in which the white cells vary in some particular from the usual type encountered, but there is no essential variation in the pathologic histology which is the court of the last judgment. There may be: (1) abnormally low white blood counts occurring often in acute leukemia, in chloroleukemia, during spontaneous remission of any leukemia, or as the result of complicating infection, benzol, X-ray or radium therapy; (2) an excessive number of myeloblasts in acute myelogenous leukemia not infrequently, in myelogenous chloroma, in the terminal stages of a chronic myelogenous leukemia or in a relapse following X-ray or radium therapy; (3) absence of neutrophilic myelocytes with great increase of the eosinophilic myelocytes at some stage of a chronic leukemia; (4) failure of the neutrophilic granules to stain in the polynuclears and myelocytes; (5) absence more or less complete of eosinophilic cells occurring early in the disease, in acute cases, with complications and as a terminal event; and (6) the same variation in the case of basophilic cells.

It must not be forgotten that severe anemias of unknown or infectious origin and that malignant tumors may produce changes in the blood picture which may suggest leukemia. The appearance of varying percentages of myelocytes in such cases, even up to twenty per cent., is not to be taken as conclusive evidence of a leukemia, especially when the total white count is low. In the acute infectious diseases of children one not infrequently finds cells of the myelocytic series in the peripheral blood. The appearance of these cells in the conditions mentioned above is regarded as due to a stimulation of the bone marrow and not as evidence of leukemia. Post-mortem examination in such cases invariably fails to show the histological proof of a diffuse disease of the entire myeloid system. Areas of myeloid proliferation may occur in the different organs with infections, but the process must be widespread and marked to be called leukemia. Cases with osteosclerosis have been reported which resemble leukemia. As a rule, however, the myeloid change in the organs has been of such low grade as to probably exclude leukemia.

The term leukanemia should be discarded. It serves merely as a cloak for ignorance and the superficial study of difficult cases. It was proposed by von Leube[196], who described a case of severe anemia which showed features of both pernicious anemia and leukemia. The red cells and hemoglobin were markedly reduced, the color index was high, while megalocytes and megaloblasts were present. The white count was approximately ten thousand with 13.6 per cent. myelocytes. The autopsy findings proved that this case was neither pernicious anemia nor leukemia, while the abscesses found in the liver and spleen with areas of necrosis in the marrow indicate that von Leube was probably dealing with a severe anemia of infectious origin in which a stimulation myelopoiesis occurred. The fallacy of classifying leukemia on a purely hematological basis is here evident and the necessity for conclusive histological proof is undisputed. If the cases in the literature reported as leukanemia are carefully scrutinized they will be found to be instances of severe infectious anemia, pernicious anemia, tumor of the bone marrow, aleukemic leukemia, or acute leukemia.

During the course of pernicious anemia large percentages of myelocytes with showers of nucleated red cells may appear producing the blood picture described by von Leube. This may occur as the result of a complicating infection as in one of our cases where pneumonia caused a rise of from 3,000 to 34,000 white cells with ten per cent. myelocytes. Post-mortem histological study showed primary anemia with slight myeloid infiltration in some of the organs, but no evidence of leukemia. The same picture has been reported in cases of carcinoma of the bone marrow.

Cases of acute leukemia with a low white count and large numbers of nucleated red cells may simulate von Leube's description of leukanemia but these acute cases all show definite and diffuse histological leukemic changes.

Another term which should be discarded is that of mixed leukemia. Since it has become generally known that there must be careful study of the large mononuclear cells in leukemic blood which show no granules to determine whether they are myeloblasts or lymphocytes there have been much fewer cases reported as of the mixed type. The so-called transition from lymphatic to myelogenous leukemia or vice versa does not occur but is described because of the same confusion existing with regard to myeloblast and lymphocyte. An acute myeloblastic leukemia with its large non-granular cells and intermediate forms (premyelocytes) may suggest a mixture of lymphatic and myelogenous leukemia. A chronic myelogenous leukemia may show an acute exacerbation with large numbers of myeloblasts. Here one might think that the type was a mixed one or that a transition from chronic myelogenous to chronic lymphatic leukemia was taking place.

Chloroma

Another instance in which confusion of classification has been manifest is seen in the case of the so-called chloroma. This condition was formerly classed with the tumors but as a result of increasing knowledge it is now believed to be a somewhat atypical form of leukemia. Indeed it is now generally conceded that chloroma is closely related to, if not a form of, leukemia. It shows a remarkable similarity to the acute types of leukemia and in many instances the clinical symptoms, the blood picture and the pathological findings are identical with those of acute leukemia. The green color of the nodules, the tendency to periosteal proliferation and the peculiar localization about the orbit, points which were originally considered as of infallible differential diagnostic value, have been found to be inconstant and therefore unreliable.

We may distinguish two types of chloroma according to the type of hyperplastic cell, (a) a myelogenous or myeloid chloroma (myelogenous chloroleukemia of Nageli[6], chloromyelosarkomatosis of Sternberg[147]) and (b) a lymphatic or lymphoid chloroma (chlorolymphosarkomatosis of Paltauf[197], chloroleukosarkomatosis of Sternberg[147], and chlorolymphadenosis of Lehndorff). Boechat[198] reviewing the literature says that twenty-one out of twenty-six cases are described as showing large lymphocytes. Since 1907 all cases reported except one have been described as showing large lymphocytes or myeloblasts. The oxydase reaction has subjected the large mononuclear cells to a more critical study and just as there has recently been an apparent increase in the number of cases of acute myelogenous leukemia over acute lymphatic so, too, there is an ever increasing number of cases of myelogenous chloroma and a diminishing group of cases reported as lymphatic chloroma.

It is difficult, indeed in certain instances impossible, to draw a sharp line between myelogenous chloroma and acute myelogenous leukemia. The presence of a green color in the nodules or the tendency to growth under the periosteum and especially about the orbit seems to be too arbitrary a standard, for cases occur in which the green pigment is absent and still others in which the peculiar proliferative growth and localization are missing, but yet green tumors are found. Again cases of acute myelogenous leukemia may show the same tendency to localization and growth as does the typical case of chloroma.

The clinical symptoms do not serve surely to differentiate myelogenous from lymphatic chloroma nor from the acute leukemias. Thus there may occur the same acute onset and rapidly progressive course with severe anemia, fever, stomatitis, ulcerative and gangrenous processes of the mouth and throat, hemorrhagic diathesis, periosteal growths and enlargement of the spleen and lymph glands of varying degree.

The blood picture is usually that of an acute myelogenous leukemia. The red blood count and the percentage of hemoglobin usually fall rapidly. The number of white blood cells is generally low at first, increasing to fifty thousand or much above, even to nearly a million. The stained smear shows large mononuclear cells, some without granules and others with a very few, typical myeloblasts and premyelocytes. Eosinophilic and basophilic cells are unusual. Nucleated red cells may be few or numerous. The red cells also show the characteristic changes in size, shape and staining reaction of a severe anemia. Some cases may have a relatively low white count throughout their course. Evidence of atypical cell formation such as marked irregularities in the shape of the nuclei of the myeloblasts may occur, identical with the changes in acute myelogenous leukemia.

The presence of oxydase or a peptic ferment in these cells is often demonstrable. A positive reaction may be of great diagnostic value as in a case which is now under our personal observation, where the blood was followed from day to day with the oxydase reaction (Graham's modification) and though negative at first, later there were found increasing number of cells with positively staining granules suggesting that the case was a chloroma of the myelogenous type.

Jacobaeus[199] describes the blood serum from a case of chloroma as greenish and states that the supernatant layer of leukocytes in a centrifuged specimen of plasma also showed a greenish tint. We have previously noted this coloration of the leukocytes in citrated blood from several cases of chronic myelogenous leukemia. This also argues for the close relationship existing between chloroma and leukemia.

The disease runs an acute course terminating fatally in less than six months as a rule. The post-mortem examination generally reveals multiple tumor-like proliferations under the periosteum, especially about the orbit, the bones of the skull, the ribs, the sternum and the vertebrae. The green color of the nodules is striking but may be absent in some cases. In some instances green areas of infiltration are found without predilection for massive growth in the subperiosteal layer of the bones. Splenic and lymph gland enlargements vary in degree. The green coloration may be slight or marked. In the bone marrow there may be diffuse or localized greenish areas of hyperplasia.

Histologically there is found evidence of a circumscribed or diffuse infiltration of the blood forming organs and in a varying degree of other organs. The myeloid system of cells is involved and the predominant cell type is generally the myeloblast although myelocytes in varying numbers may occur. The proliferation is frequently of such high grade as to resemble true tumor growths. The lymphatic system does not share in the hyperplasia.

Pseudoleukemia

In the present state of our knowledge it does not seem profitable to discuss in further detail other conditions related to leukemia. Many of the cases of pseudoleukemia (Pappenheim, Cohnheim[200]) and the aleukemic myeloses and lymphoses, as has been suggested above, have not been sufficiently studied to determine with certainty whether they should be considered as leukemia or as tumors. A certain proportion of such cases are doubtless instances of leukemia in a subleukemic or aleukemic stage while others are undoubtedly tumors of lymphoid or marrow tissue. The so-called lymphosarcomatoses and the myelomata must at present be regarded as tumors.

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CHAPTER XVIII

POLYCYTHEMIA

By R. FITZ

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INTRODUCTION

Polycythemia is the name for a condition of the blood in which the number of red corpuscles is increased above the normal average of five million per cubic millimeter. In a clinical sense, however, the term is ordinarily used for cases described under the group "erythremia."

As early as 1854, Vogel[1], the first systematic investigator of the blood, demonstrated that the number of red cells was increased in certain diseases and that such polycythemia was relative when it depended upon concentration of the blood in red corpuscles and absolute when the total bulk of red corpuscles in the body was greater than normal. In 1872, when accurate blood studies were begun by Malassez[2], Naunyn[3] pointed out that an increased hemoglobin concentration occurred under several physiological and pathological conditions, notably in chronic heart disease with cyanosis. A few years later physiologists became interested in the factors influencing the composition and number of the red cells, and in 1890, Viault[4] studying the bloods of normal men and animals living at high altitudes found they were constantly polycythemic. In 1892, Vaquez[5] reported a case of peculiar cyanosis with persistent polycythemia and an enlarged spleen. The condition was so striking and unusual that he suggested it was due to a disease depending on a primary hyperplasia of the erythroblastic bone marrow. His observation was confirmed in 1899 by Rendu and Widal[6] in France, in 1902 by Türk[7] in Germany, and in 1903 and 1904 by Osler[8] in America and Great Britain. These papers stimulated an immense amount of work in polycythemia in all four countries with the result that in recent years the subject has been thoroughly studied from several points of view. Individual cases and groups of cases with autopsies have been reported emphasizing the clinical aspects, course and pathological anatomy of polycythemia; observations have been recorded on the morphology, and the chemical and physical characteristics of the blood in this condition; the effect of polycythemia on gaseous and total metabolism has been demonstrated; and experimental polycythemia has been produced and studied in animals.

It is obvious that polycythemia, or merely an increased number of red corpuscles per cubic millimeter of blood, is not a disease in itself but rather a sign of an abnormal condition within the body. It may occur in normal individuals as the result of physiological stimuli, or in disease as the result of pathological stimuli of determined or undetermined cause. Polycythemia may be relative in the sense of Vogel when the blood volume is concentrated and there is no real over production of red corpuscles, or absolute when the total number of corpuscles in the body is actually increased. By analogy with the terms leukemia and leucocytosis, cases of absolute polycythemia include those of erythremia which appear to be due to an essential and primary disease of the erythroblastic bone marrow and those of erythrocytosis which result as a secondary and symptomatic hyperplasia of the red cells. Relative polycythemia is usually transitory and unimportant. Absolute polycythemia, both as erythremia and erythrocytosis, deserves the fullest consideration.

Relative Polycythemia

Relative polycythemia may occur in normal individuals as the result of unusual water excretion through the skin and lungs, after violent exercise, or from sweating induced by hot air baths. It occurs in disease from any condition which causes blood concentration, such as continued vomiting or chronic diarrhea, and has been reported as a complication of diabetes insipidus. The diagnosis depends upon the presence of an increased red cell count in the blood combined with evidence of diminished blood plasma volume, such as may be obtained most simply by the hematocrit. The condition is usually transitory and can be often cured by dilution of the blood with fluid. It has no characteristic symptoms or physical signs and, on the whole, is not of great clinical significance on its own account.

ABSOLUTE POLYCYTHEMIA

I. ERYTHREMIA

Erythremia is a disease of unknown origin characterized by persistent polycythemia due to excessive erythroblastic activity of the bone marrow, usually by a red or ruddy appearance of the patient, and is often accompanied by an enlarged spleen. In the literature it has also been called splenomegalic polycythemia, myelopathic polycythemia, polycythemia vera, polycythemia rubra, polycythemia with chronic cyanosis, erythrocytosis megalosplenica, Vaquez's disease, and Osler's disease.

It affects persons of either sex, chiefly between the ages of 35 and 50, but has been observed in persons after 60 and before 30 years of age. It occurs in all races and nothing is known as to the relation of the condition to the atmospheric pressure or climate, nor have any predisposing causes been demonstrated. It is not as rare a disease as was first supposed, since Lucas[9] collected 149 unquestionable cases from the literature in 1912, and many more have been subsequently reported.

Symptoms of Erythremia

It is difficult to obtain any information as to the date of onset of the illness in patients with erythremia because the disease is usually well developed before any symptoms are noted. In members of the family of a patient with erythremia having symptoms, others are found with increased blood counts without symptoms and these may remain symptomless for a long time. Eventually, in some cases at least, a varied symptomatology develops. The first complaint is often the abnormal color of the skin and mucous membranes which the patient has noticed himself. Eye symptoms are common and frequently the first noted, the patient complaining of blurring of vision or that he is disturbed by specks before his eyes. The mentality may be abnormal with periods of irritability and depression, or the speech may be embarrassed and the memory poor. The digestive system is often involved. Obstinate constipation is common, as is loss of appetite, a feeling of fullness in the stomach, and attacks of vomiting without relation to meals. There may be attacks of lumbar pain ending with paroxysms of hematuria lasting for four or five days. Menstruation may be irregular. Such general symptoms as weakness, lassitude, loss of weight, shortness of breath on exertion, easy fatigue and somnolence are common. Pain in the legs may be a striking symptom, occurring as violent muscular spasms or in the form of paresthesia with hyperidrosis. The pain may be so severe as to keep the patient awake at night and may be accompanied by swelling around the large joints suggesting infectious arthritis. Bleeding is not unusual, occurring as hemorrhage from the nose or gums, from the stomach, into the pleural and peritoneal cavities, and into the brain, or as purpura or large subcutaneous hemorrhages.

Physical Signs in Erythremia

The physical examination of patients with erythremia is more characteristic. On inspection, the skin, especially of the face, hands and feet is usually a reddish blue color rather than that of a true cyanosis, although some cases are pale rather than high colored. Exposure to cold may intensify the reddish color, while a warm room occasionally causes blueness. In long standing cases the skin becomes pigmented and may be a violet or almost black color; angiomatous nevi may appear in great numbers. At times a curious slate-gray color appears. The conjunctivae are notably blood-shot with their veins full and prominent. The tongue is bluish red and the mucous membranes of the mouth, fauces and larynx are deeply congested. The subcutaneous veins in the face, arms and legs are often prominent, especially when the patient is in a warm room or in bed. Edema of the legs may be present.

In typical cases the body temperature is not elevated. The pulse is slightly faster than normal, but regular and of good quality. The heart is not enlarged to percussion nor are the sounds abnormal. The peripheral arteries are not thickened or tortuous. The blood pressure is usually normal although in a certain type of cases it is elevated. The lungs are normal. The abdomen may be full and slightly distended, with tenderness in the left upper quadrant. The liver edge is barely palpable, although the liver dullness is slightly increased suggesting a trivial enlargement. The spleen as a rule is enlarged, but varies in size from being just palpable to a mass extending to the umbilicus. The veins of the fundus oculi are voluminous and engorged so that they appear much larger and darker than the arteries, and are tortuous or even show true varicosities. Small areas of hemorrhage sometimes are seen without exudate. The disc is normal or perhaps slightly reddened. Such congestion has been considered typical by various authors and almost all agree on emphasizing the importance of this feature of the physical examination. Slight palsies of one or more cranial nerves have been frequently observed. The reflexes, both superficial and deep, may vary on the two sides of the body, and localized areas of anesthesia or paresthesia are found frequently.

Routine laboratory study of cases of erythremia exhibit the following features. The Wassermann reaction in blood serum is negative. The amount of urine in cases not complicated by renal hemorrhage may be normal or scanty. Albumin in variable quantity is usually present and the sediment contains hyaline and granular casts with or without a certain number of red corpuscles. At times the urine is so abnormal as to suggest a co-existent nephritis, an impression born out by evidence of renal insufficiency in functional kidney tests. In one of Bock and Means'[10] cases* the output of phenolsulphonephthalein was diminished, Ambard's constant was increased, there was a fixation of gravity and the excretion of sodium chloride was interfered with. However, such findings were transitory. With rest and a restricted diet, these signs cleared up and renal function became normal, to grow worse again from time to time without more definite symptoms of nephritis. The stools are normal except in cases with gastrointestinal hemorrhage.

The Blood in Erythremia

The blood is essentially pathological. The total volume is increased to a considerable extent as has been demonstrated in several cases by Haldane and Smith's[11] carbon monoxide method. The reported figures vary somewhat but have reached as high as three times the normal figure corresponding to the patient's weight. Keith, Rowntree, and Geraghty[12] reported a simpler method for estimating blood volume, in 1915, by the use of the dye, vital red. According to their results the normal blood volume is larger than is estimated by Haldane's method, so that data from the two methods are not strictly comparable. However, the two cases studied by Bock and Means confirm the older observers. In one case the blood volume by the vital red method was 8,545 c.c., or 124 c.c. per kilogram of body weight instead of the normal of 85 c.c. In the other, blood volume was 6,659 c.c., or 118 c.c. per kilogram of body weight. Such an increase in blood volume is almost entirely due to the increased bulk of red cells, and not due to an increase in the blood fluid. This can be demonstrated by the hematocrit as well as by the total plasma volume. Normally the corpuscles represent about 46.8 per cent. and the plasma about 53.2 per cent. of a volume of blood, while the total plasma volume is between 42 and 56 c.c. per kilogram of body weight. In erythremia, if the blood is allowed to stand for several hours, almost no plasma comes to the surface, and if the hematocrit is used, the figures may become 73 per cent. of cells and 27 per cent. of plasma. In Bock and Means' two cases, in addition, the readings for the total plasma volume per kilogram body weight were 50 c.c. and 39.6 c.c. respectively.

The hemoglobin content of the blood is always higher than normal, the degrees in increase observed depending in large measure upon the method used for estimating it. In the majority of reported cases it has

*This case was autopsied. There was no evidence of chronic nephritis.

ranged between 125 and 150 per cent., though in one of the cases of Bock and Means it reached 220 per cent. by Palmer's[13] method. It has been suggested that such increased hemoglobin was not normal in the amount of oxygen it would take up and as a result stimulated a compensatory overproduction of red cells. How true this is, is uncertain. According to Lutenbacher's[14] analysis of the literature on the subject the best evidence shows that in erythremia the hemoglobin combines normally with oxygen and bears a normal ratio to the oxygen capacity of the blood. Associated with such a high hemoglobin content is an increased red count which has been reported as being approximately the same in the arteries, veins and capillaries. The counts quoted vary considerably in different cases and may vary from time to time in the same case but are usually between 7 to 10,000,000 per cubic millimeter of blood, while one count of 14,800,000 has been recorded. The white corpuscular count is usually increased to about 15,000 cells, or more, per cubic millimeter. In some cases, however, the number of white cells is normal or even diminished.

Morphologically, the blood is dark red and appears thick. Stained films show, according to Vaquez, that the average diameter of the red corpuscles is about the normal figure of 7 micra. Careful study, however, usually reveals the presence of occasional normoblasts and that the corpuscles as a whole have more than the normal variation in size and shape, while a few are polychromatophilic. The blood platelets have been reported increased, normal and diminished; discrepancies suggesting that their number has not been estimated in enough cases or by sufficiently accurate methods to warrent any conclusion. Of the white cells, the neutrophils are said to be relatively increased and the lymphocytes diminished. Occasional cases have been reported where mast cells, eosinophils and myelocytes were observed constantly in large enough numbers to justify mention.

The coagulation time of the blood varies, being increased or diminished without relation to the number of red cells per cubic millimeter or to the percentage of hemoglobin. The color index is reduced.

Experiments with salt solution or hemolytic sera have not demonstrated that the fragility of the corpuscles is abnormal. On the other hand, the few observations recorded on the excretion of bilirubin in urine and feces, using the total as an indication of blood destruction, tend to show that the destruction of red cells in erythremia is not diminished to any extent, but if anything is increased.

The physical characteristics of the whole blood show that the viscosity is much increased, the specific gravity is abnormally high, while the freezing point and spectroscopic examination is normal. The specific gravity of the serum is normal and its refractometric index has been reported as abnormally low, suggesting that the colloids of the serum are not increased.

The chemical characteristics of the whole blood vary in proportion to the increase in corpuscles. The total non-protein nitrogen, fat, uric acid and iron per 100 c.c. of whole blood is definitely increased while the sugar concentration is slightly above normal. In the plasma these various substances are in approximately normal concentration. These facts are of clinical significance in that it is possible to misinterpret the various chemical analyses, which are ordinarily reported as grams or milligrams of substance per unit volume of blood, unless the increase in the blood and corpuscular volume is taken into consideration.

The effect of such a condition of the blood on the body as a whole is naturally of great interest. Nitrogen metabolism, as studied in a few cases which were given an analyzed diet, has been normal. Gaseous metabolism was observed first by Senator[15], whose findings have been subsequently confirmed. As a rule the basal metabolism is increased slightly, but without any obvious relationship to the total blood volume or to the hemoglobin content of the blood. The underlying reason has not been explained.

The volume of air breathed per minute tends to be increased, as shown in the cases reported by Senator and by Means and Bock, which varied between 8 to 5 liters and 11 to 5 liters, figures considerably in excess of the average normal. Thanks to such ventilation, the arterial blood is normally saturated with oxygen (98 per cent. in Senator's case and in that of Bergmann and Plesch[16]), or approximately so (96 per cent. and 93.3 per cent. in the cases of Means and Bock), so that owing to the increased blood volume the total oxygen in the arteries is much increased. The need of the cells is no greater than normal, therefore, the venous blood is almost as rich in oxygen as is normal arterial blood, and the "coefficient of utilization" of oxygen is much reduced. Röver[17] found in one case, which died shortly afterwards, a remarkably low "coefficient of utilization" and attached great prognostic significance to the finding. His observation has not been confirmed.

The increased blood volume in erythremia does not cause a marked change in the volume output of blood from the heart. Senator reports a case in which it was 65 c.c. to the minute, Bergmann and Plesch one of 54 c.c., and Means and Bock one of 71 c.c., all showing a normal or abnormally high cardiac output. However, as the blood volume is so much increased and the rate of flow approximately normal, the circulation as a whole is relatively sluggish and there is considerable stasis.

On the whole, clinical and laboratory studies of patients with erythremia have shown that the disease is one of unknown origin in which the total volume of blood corpuscles is increased while the plasma volume is normal or slightly subnormal. Physical and chemical analyses of the blood show that the plasma or serum is not remarkable in any respect. The red corpuscles are increased both in volume and concentration per unit volume of blood. As a result, the viscosity and specific gravity of the whole blood is high. The individual corpuscle is, so far as is known, normal in respect to its chemical and physical reactions. Abnormal red cells are seen in the circulation as shown by variation in the size and shape of the cells and by the presence of normoblasts or cells with polychrome granules. That the excess of red cells is not due to any abnormality in the life of the individual corpuscles is shown by the lack of evidence of increased fragility or of diminished destruction. Final evidence that the disease is primarily in the bone marrow is the co-existent leucocytosis usually found, which is due to a relative increase in white cells of the polymorphonuclear series with the occasional presence of young leucocytes, such as mast cells or myelocytes.

Course of the Disease

The course of the disease is chronic, lasting for years and tending to spontaneous remissions and exacerbations, but is eventually fatal. Patients usually die from intercurrent diseases. Some have died in a sudden exacerbation of cyanosis, others from complications due to vascular disease, such as cerebral thrombosis, cerebral hemorrhage, or hemorrhage from a gastric varicosity.

Pathological Anatomy and Physiology

The most striking feature of the pathological anatomy of erythremia is the enormous injection of all blood vessels in the body. The spleen, though usually enlarged from engorgement with blood, does not show any characteristic lesions and is normal histologically. Tuberculosis of the spleen, which was thought by Rendu and Widal to be a significant factor in the disease, is rarely present. The bone marrow presents the characteristic picture by which an anatomical diagnosis is possible. Grossly, it retains its fetal red appearance in almost all bones. Microscopically it shows, in addition to congestion, hyperplasia of all blood cells of both the erythrocytic and leucocytic series. The other organs are essentially normal except for their great vascular engorgement which may lead to hemorrhage in the stomach or elsewhere, or to minute or larger thromboses in the nervous system or other parts. A certain amount of pulmonary emphysema, arteriosclerosis, fibrosis of the cardiac muscle, renal disease, and the results of disease of the cerebral vessels have been noted in a few cases but not constantly.

Most of the signs and symptoms of erythremia may be accounted for by the bone marrow findings at autopsy. The increased blood volume resulting from the primary disease probably causes dilation of the capillaries and eventually degenerative changes in the vascular system leading to true passive congestion, cyanosis, bleeding from the gums or elsewhere, and thrombosis or other local circulatory disturbances. As Weber[18] has suggested, an elaborate vicious circle is established; the polycythemia tends to impede the circulation and the blood stasis thus produced favors cyanosis and increases the circulatory difficulty by giving rise to a compensatory erythrocytosis in addition to the primary erythremia.

More exact knowledge as to the nature or cause of the disease is lacking. It seems possible that it is allied to leukemia, as suggested by Blumenthal[19]. He reported the case of a woman whose history suggested erythremia. Her blood had 110 per cent. of hemoglobin and 11,450,000 red cells with an associated leucocytosis of 16,300 of which 45 per cent. were myelocytes. After death the leucoblastic elements of the bone marrow were found to exceed the erythroblastic elements so that the bone marrow resembled leukemia more than erythremia. Rosin's[20] case is similar. At the first observation, the red count was 10,000,000, dropping subsequently to 3,500,000, while a leucocytosis of 52,000 developed. Winter[21] suggests the converse of this in a case of myelogenous leukemia having at first observation 4,000,000 red corpuscles and 22,600 leucocytes. Three years later the patient had 8,000,000 red cells and the white count was unchanged.

Atypical Erythremia

Atypical cases of erythremia with the clinical and laboratory findings already described have been subdivided into various groups by different authors. One which has been emphasized is the group of cases without enlarged spleen. Another includes those cases which appear to be congenital or to develop in early life. A third is the polycythemia hypertonica of Geisböck[22]. This is an erythremia occurring in elderly patients with hypertension. The spleen is not enlarged. The heart is hypertrophied and the urine has a low gravity and a trace of albumin so that physical examination suggests arteriosclerosis with cardiac enlargement and nephritis. The blood, however, shows the picture of true erythremia. The red count varies between 8 and 11,000,000 cells and is alike in arteries, veins and capillaries. The specific gravity of the blood serum is normal, showing that the polycythemia is not due to blood concentration. Cerebral hemorrhage often causes death. It has been questioned whether or not this group of cases should be classified as true erythremia. It would seem reasonable to agree with Orlowski[23] and believe that the condition represents a combination of erythremia and arteriosclerosis with hypertension.

Diagnosis of Erythremia

The diagnosis of erythremia is suggested by the cyanotic appearance of the patient and the history of giddiness or ringing in the ears and other vague symptoms. It depends upon the recognition of persistent absolute polycythemia and the absence of any obvious cause for it. Splenomegaly, if present, makes the clinical picture more suggestive, but may give rise to difficulties in diagnosis if it occurs in association with conditions causing erythrocytosis, such as chronic heart disease or syphilis. It would seem that the individual case would have to be worked out thoroughly along the lines of pathological physiology which have been outlined, before certain conclusions can be reached.

Treatment of Erythremia

Inasmuch as the course of erythremia is always chronic with periods of improvement and remission it is difficult to outline any particular form of treatment with enthusiasm. It seems certain that splenectomy does no good and may do considerable harm. Temporary benefit has been obtained in certain cases through repeated bleedings or oxygen inhalations. Radium and X-rays have been used with apparent benefit in some cases, and with no effect in others. McLester[24] used benzol in one case with striking and immediate benefit. His reason for the use of the drug seemed logical, as experiments with animals have shown that it caused reduction in both the red and white blood cell counts owing to diminished blood formation in the bone marrow. Hurwitz and Falconer[25] reported a case which improved under a combination of X-ray treatments with benzol. Their suggestion was that X-rays might act in a more destructive manner on the erythropoietic tissues which were rendered less resistant beforehand by the toxic action of benzol. Against the drug are the facts that it is dangerous because of its poisonous action on the bone marrow, that it is apt to cause gastrointestinal disturbances, and many of the cases of erythremia treated with it have shown no improvement.

The most sensible and conservative treatment would seem to be the establishment of a simple form of life with avoidance of undue strain upon the vascular system, such as might be caused by physical or mental overexertion or by the abuse of alcohol, tobacco or coffee. A simple diet, on purely theoretical grounds, might be prescribed, containing little meat or vegetables rich in iron; the patient should be advised to lead the simple life of a chronic cardiac or nephritic case. X-rays and radium or some other treatment designed to diminish the production of red cells may be tried as an experiment but without much probability of doing good or effecting a cure.

II. ERYTHROCYTOSIS

Erythrocytosis is a condition of the blood characterized by a persistent absolute polycythemia which is secondary to a known cause and usually represents an effort on the part of the organism to compensate for difficulties in the oxygenation of the blood or tissues of the body. The best known clinical forms of erythrocytosis are those due to diminished oxygen in the inspired air such as is obtained at high altitudes, and those due to imperfect oxygenation owing to pulmonary disease and to circulatory disturbance in cardiac disease. Careful studies have been made, in addition, upon erythrocytosis due to various drugs and toxins of other sorts.

Erythrocytosis of High Altitudes; Altitude or Mountain Sickness

The erythrocytosis of high[26] altitudes or that due to diminished oxygen of the inspired air under laboratory conditions is accompanied by a train of symptoms known as *Altitude* or *Mountain Sickness*. There are two forms of this disease. The acute type, which has recently become of great importance to aviators, begins suddenly when a sensitive individual enters too rarified an atmosphere of air. The chronic type, which has been studied by mountain climbers, has a more gradual onset. In each, the characteristic symptoms are headache, giddiness and dyspnea on exertion, nausea, vomiting and, especially, a sense of physical prostration at the prospect of any effort. If the patient returns to conditions of normal atmospheric pressure these manifestations pass off quickly. If he remains at a high altitude the symptoms grow worse until finally he loses all will power, and often dies from inability to make the attempt of moving out of danger. An important complication is hemorrhage from the lips, lung, or intestines, and into the conjunctivae.

The disease as a whole has been studied by physiologists in themselves, or in animals on different mountain peaks, or at an artificial altitude made from rarification of the sea-level air. Changes always occur in the blood. Even if a normal man ascends passively to 14,000 feet above sea-level his blood within twenty-four hours shows an increase in hemoglobin concentration and in the number of red cells per cubic millimeter. This reaches its maximun in from two to four days but is followed during several weeks by a further increase in the amount of hemoglobin and cells. The initial rise depends upon the development of a relative polycythemia due to concentration of the blood so that the total blood volume is diminished, and upon the fact that there appear in the systemic circulation, suddenly, a large number of corpuscles which are ordinarily side-tracked and inactive. The more gradual increase in the red count is due to an absolute polycythemia in which the total blood volume is increased.

The hemoglobin percentage, after continued residence at a high altitude, may reach 135, and the red count 7,000,000 cells per cubic millimeter; the leucocytes are not increased to any extent. Morphologically the red cells show variation in size and shape, tend to be smaller than normal and occasional nucleated cells are seen. The lymphocytes are relatively increased as is the ratio of platelets to the corpuscles. Observations on the coagulation time, and fragility of the corpuscles have not been reported nor have the physical and chemical properties of the blood been studied, except that it is known that the blood viscosity is increased and that the specific gravity of the whole blood increases in amount parallel to the increase in corpuscles and hemoglobin, while the specific gravity of the plasma remains normal. Anatomical evidence from animals killed at altitudes as compared with similar animals killed at sea-level suggests that this blood picture is due to an over-production of cells and that it is not due to any abnormality in the life of the individual corpuscles. The marrow from animals living in low oxygen tension is redder than normal, shows unusual activity in the young cells of the erythrocytic series and has a decreased amount of fat.

The effect of high altitudes on the body as a whole results in abnormalities in metabolism. Nitrogen excretion tends to be increased as the oxygen tension of the air diminishes, though at moderately high altitudes nitrogen may be spared and stored in the body. Basal metabolism is distinctly increased, the degree of increase varying in different individuals and bearing no relation to either altitudes or to the polycythemia. Striking changes occur in respiration and in the rate of blood flow, both pulmonary ventilation and the minute output of the heart being markedly increased.

The explanation of these findings lies in the diminished oxygen tension of the inspired air. In order to oxygenate its tissues normally, the organism is forced to increase its total oxygen carrying powers. It does this in three ways: by an increased number of red corpuscles and increased amount of hemoglobin, thus providing for more oxygen per unit volume of blood; by greater ventilation of the lungs, which permits a more thorough saturation of the hemoglobin than would be possible if the oxygen pressure in the lungs decreased proportionately to the fall in barometric pressure; and by a more rapid rate of blood flow, which raises to a limited extent the oxygen pressure in the blood passing through the tissues. Why the basal metabolism should be increased is not clearly explained.

Erythrocytosis of Chronic Cardiac and Pulmonary Disease

The erythrocytosis which occurs in chronic cardiac and pulmonary disease is also an absolute polycythemia and a compensatory reaction on the part of the organism. As in the other absolute polycythemias, the blood volume and the total amount of hemoglobin and of red corpuscles are increased, the color index is reduced, the specific gravity and viscosity of the whole blood are abnormally high, and the bone marrow at autopsy is red and hyperplastic. The red cell count may reach nearly as high figures as in erythremia but the cells are not so equally distributed, being distinctly less numerous in the arterial blood than in the venous or capillary blood.

An interesting fact in regard to erythrocytosis in heart disease is that it often accompanies congenital heart lesions or lesions acquired in early life and is less frequent in older people. One probable explanation is, according to Senator, that the cells of young people are better nourished, more resistant and more reactive to stimulation than are the tissues of older people, which are poorly nourished and unresistant owing to circulatory changes.

The cause of this type of erythrocytosis in cardiac disease is well demonstrated by two cases of mitral stenosis reported by Means and Newburgh[27]. At the time of study both were compensated, one having moderate cyanosis without dyspnea, the other having marked cyanosis and dyspnea on the least exertion. The first case had a hemoglobin percentage of 120 and the second of 113, justifying the deduction that both were polycythemic. The basal metabolism was not increased in either case. The pulmonary ventilation was 9.4 and 9.5 liters of air per minute. The volume output of the heart per beat, however, was only 27 and 17 c.c. against the normal controls of about 50 c.c. and the "coefficient of utilization of oxygen" was very high. In other words, since the circulation was slowed by the diseased heart, an excessive proportion of oxygen was used up in the systemic capillaries and the cells suffered from oxygen want. This was compensated for by an increased pulmonary ventilation and by an increased total amount of hemoglobin. It would be interesting to study similar cases through different stages of compensation and decompensation in order to determine how quickly the erythrocytosis disappears when the circulation rate becomes normal. The rapid hemoglobin changes observed by Lundsgaard[28], in certain of the cardiac cases reported in his studies on oxygen in the venous blood, suggest that pronounced and sudden changes in blood volume may frequently complicate the clinical course of chronic heart disease.

The erythrocytosis due to chronic pulmonary disease is analogous to that produced by diminished oxygen in the inspired air, except that the lungs are at fault and not the air. The arterial blood cannot be completely saturated with oxygen on account of diseased lung tissue, so that a compensatory number of red cells and amount of hemoglobin is necessary to carry a normal amount of oxygen to the cells. Hürter's[29] observations in this connection are of interest. Normally the degree of oxygen saturation of the arterial blood, according to Barcroft's method which was used in the observations quoted, is about 94 per cent. In four patients with compensated heart lesions the saturation was 90, 100, 90 and 95 per cent.

One patient with diffuse bronchitis showed 94 per cent. and another with phthisis 88 per cent. Two patients with lobar pneumonia showed 81 per cent. and 79 per cent. saturation. In other words, the compensated heart cases oxygenated their arterial blood normally. The cases with pulmonary lesions reacted in regard to the saturation of their arterial blood as do cases in a rarified atmosphere, and a similar train of blood and respiratory changes would be natural. That such changes occur in the blood, at least has been suggested by Stadie[30], who found that the hemoglobin percentage of the blood was unusually high in cases of bronchopneumonia with a marked degree of arterial unsaturation. This was possibly due to a compensatory polycythemia and not, as he surmises, to blood concentration alone.

Erythrocytosis Due to Other Causes

A variety of other causes may induce a secondary polycythemia. Lamson[31] made a careful review of the literature on the known causes of polycythemia and has listed, among others, the following conditions and substances which have been found by different investigators to increase the number of red cells per unit volume of blood: tuberculin, thorium X, sulphur, strophanthin, sodium nitrate, radium chloride, pituitrin, pilocarpin, phosphorus, opium, nicotin, epinephrin, digitalis, carbon monoxide, caffein, arsenic, liver disease, lung emboli, asphyxia, massage, exercise and emotional stimuli.

The majority of these agents seem to produce the increased red count by their toxic action upon the corpuscles as a result of which the oxygen capacity of the blood is reduced and a compensatory overproduction of corpuscles occurs. They act to a less degree by direct stimulation of the bone marrow itself. Finally, Lamson, in a series of carefully conducted experiments, has demonstrated that the acute polycythemia which follows the injection of adrenalin results through stimulation of the liver, by which a large number of corpuscles normally stored there are brought into the general circulation, and is not due to an overproduction of new cells. The clinical bearing of his experiments has been demonstrated in the acute polycythemia found at altitudes. It is possible that future work in regard to other acute polycythemias will show that the liver is of greater importance as a storing place of red cells than has been hitherto recognized.

In summary, therefore, there are three well defined causes for erythrocytosis. The first depends upon defective saturation of the arterial blood with oxygen, the second upon slowing of the circulatory rate so that an excessive proportion of oxygen is used up in the capillaries with resultant oxygen want in the tissues, and the third upon a defect in the hemoglobin of the blood so that it is unable to combine with oxygen in normal amount.

The immediate effect of any of these stimuli is probably identical with that observed by Lamson experimentally, namely, stimulation of the liver by which red cells stored there are suddenly freed into the general circulation until a sufficient number of new corpuscles can be formed to compensate for the new needs of the organism. The ultimate effect is to cause an absolute polycythemia. Inasmuch as oxygen want is the fundamental cause of the increased blood production in all these cases, it would seem logical to believe with Haldane[32] that, although the most advantageous method for its administration is not yet certain, oxygen has a far wider and more important field for treatment in erythrocytosis than was previously suspected. Otherwise there is no specific remedy beyond attempting to improve or remove the underlying process which produces the symptom complex.

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CHAPTER XIX

PURPURA AND ALLIED CONDITIONS

By HENRY A. CHRISTIAN

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INTRODUCTION

It seems worth while to discuss purpura from a dual viewpoint; first, as a definite blood disturbance which results in certain clinical manifestations (purpura hemorrhagica); second, as one of a group of skin lesions, having much in common and associated with general or visceral disturbances that give important symptoms. It is not possible today to say how many of the cases grouped under the second heading have characteristic blood disturbances; some have a similar blood picture to that found in purpura hemorrhagica but most do not; in most of them the blood, so far as has been detected, presents no departure from the normal.

PURPURA HEMORRHAGICA

Definition and Pathological Physiology

Purpura hemorrhagica has been defined by Minot[1] as a condition characterized by hemorrhage from the mucous membranes, petechiae or ecchymoses of the skin, a markedly reduced platelet count, a much prolonged bleeding time and a non-retractile blood clot. The cause of the hemorrhages seems to rest in the platelet deficiency, though it would seem that there is some associated lesion locally of the small blood vessels. When the cause of the platelet deficiency is unknown, we speak of cases of idiopathic purpura hemorrhagica; when the platelet deficiency is due to or associated with some recognized disturbance, we speak of the condition as secondary or symptomatic purpura hemorrhagica.

The origin of the blood platelets is in the bone marrow by budding off from the megacaryocytes (Wright[2]). Blood platelet deficiency can come about either from any cause that destroys the platelets very rapidly after their formation, or from any cause that stops their formation from megacaryocytes, or from any cause that destroys the megacaryocytes themselves. There is evidence that both the first and last of these processes actually takes place; the second may occur but has not been positively demonstrated.

If the cause of the platelet deficiency lies in a rapid destruction of the platelets after they are formed, their process of formation may be normal and the megacaryocytes in the bone marrow be found in the usual number and of normal appearance. This might occur without there being any increased destruction or abnormality in formation of the other elements of the blood. If so, the bone marrow would be essentially normal, and apart from deficiency in platelets the blood would show no other changes than those following hemorrhage, and these would be in ratio to the amount of blood lost as a result of the purpura and to the acuteness or chronicity of the incident hemorrhage. In other words, here the blood picture would be that of a post hemorrhagic anemia plus a low platelet count. The red blood cells would be decreased in number, the color index would be lowered and young forms would appear in the circulation. Leucocytes would be normal or moderately increased. There would be no signs of blood destruction. Minot[3] refers to a case presenting these characteristics and autopsy on which showed a red marrow with evidence of active regeneration of the red and white cell elements and normal looking megacaryocytes in normal or moderately increased number in the bone marrow. Lee and Robertson[4], found essentially the same condition in experimental purpura hemorrhagica in rabbits produced by injections of an antiplatelet serum. Their work is in continuation of observations made by Le Sourd and Pagniez[5], and by Ledingham and Bedson[6]. This has been recently discussed by Watabiki[7]. Unfortunately we have no way of determining whether platelets are being destroyed in the circulation or not; so in a patient with purpura hemorrhagica we might find all of the phenomena described above in case the platelet deficiency was due not to accelerated platelet destruction, but to an inability of megacaryocytes to bud off new platelets. The evidence for platelet destruction rather than defective formation by budding off lies in the animal experiments, but these do not justify denying the possibility or even probability of the latter mechanism, namely, defective formation of platelets with a normal number of normal appearing megacaryocytes in the bone marrow. In patients with purpura hemorrhagica neither increased lability of the platelets nor any abnormal destructive power of the blood serum on platelets from normal persons has been demonstrated.

If purpura hemorrhagica is caused by platelet deficiency and some condition arises which interferes with bone marrow function by injuring all of the bone marrow cells, megacaryocytes, hematoblasts, and myelocytes, on theoretical grounds we should have purpura hemorrhagica, anemia, and leucopenia. Such a process of unknown origin is met with in aplastic anemia, and in aplastic anemia usually there are hemorrhages giving a secondary or symptomatic purpura hemorrhagica. The blood picture here is one of quite normal-looking red cells: the count is low; the color index is about 1; there are no evidences of red cell regeneration or of red cell destruction; there is leucopenia with absolute diminution of polynuclears, disappearance of eosinophils, and a relative lymphocytosis; platelets are decreased in number. The difference between aplastic anemia and idiopathic purpura hemorrhagica lies in the signs of a general bone marrow aplasia in the former, with hyperplastic ability in the latter except for platelet production, or if platelets are formed they are quickly destroyed. The low platelet count is the point of similarity in the two, and this presumably explains the hemorrhagic tendencies of each.

Now if we can have a process which destroys all bone marrow activity and causes typical aplastic anemia and one that affects only the formation of platelets and causes idiopathic purpura hemorrhagica, it is likely that intermediate or mixed processes will occur, and these serve to explain atypical or intermediate cases, where with decreased platelet count there are signs of depression or aplasia of either or both the white and red cell elements of the marrow.

Just the same end-result as to platelets will happen if, instead of some toxic substance destroying megacaryocytes and other bone marrow elements, the megacaryocytes are crowded out. This happens in some cases of leucemia leading to a low platelet count, anemia and a hemorrhagic tendency, another example of secondary or symptomatic purpura. Bone marrow tumors may in a similar way produce purpura. Certain toxic substances in animals and in man may cause bone marrow aplasia and purpura. Benzol is such a substance. Similar conditions may be brought about by bacterial toxins, usually after a primary period of hyperplasia of the bone marrow followed by exhaustion and a terminal aplasia. It may occur in late bone marrow exhaustion in pernicious anemia.

In the pathological physiology of purpura hemorrhagica, as well as in the effects of blood transfusion in the condition, the quite short life of the platelets after formation enters. This is considered to be from three to five days[8] in contrast to a life period of from ten to fifteen or more days for red cells in the circulation. If transfused blood does not institute renewed activity in platelet formation its effect, so far as influencing hemorrhage is concerned, will be necessarily a brief one; if hemorrhage is stayed for more than a very few days it is evidence that bone marrow or other changes have taken place restoring platelets to a condition, temporarily at least, normal or approximating normal. If some toxic activity occurs injuring extensively all bone marrow elements, platelet reduction because of their short life will precede red cell and white cell reduction and purpura (hemorrhage) will occur early in the stage of aplastic anemia before there is much evidence of anemia. Such cases are seen. Ordinarily megacaryocytes are more resistant to degenerative influences than other bone marrow elements, and so platelet reduction is late in development and evidences of marked anemia antedate purpura (hemorrhage).

This brief discussion of the pathological physiology of platelets will serve to give a better understanding of the various clinical types of cases encountered in the purpura-anemia group of blood disturbances.

Etiology

The cause of the condition is unknown. While purpura occurs with infections of various sorts bacteriological study of purpura hemorrhagica as well as animal inoculations are not confirmatory of the idea that it has an infectious origin.

The Blood in Purpura Hemorrhagica

Platelet reduction is the most characteristic feature. This was noted as early as 1887 by Denys[9]. Hayem was the first to note reduction of actual platelet counts. Pratt, Duke, Minot and others have contributed numerous observations of actual platelet counts in individual cases. Different methods of counting platelets give somewhat different results, so in comparing actual counts the method used needs to be taken into account. Hayem's method gives as a normal number 250,000 per cubic millimeter; Pratt's method 469,000. In purpura counts considerably below 5,000 have been reported by Duke[10], by Minot[1], by Pratt[11], and by Selling[12]. According to Minot[3], when the platelet count falls below 60,000 per cubic millimeter hemorrhage tends to occur, and when the bleeding in purpura hemorrhagica is severe the platelet count is a very low one. Conversely, with improvement, whether spontaneous or due to transfusion, the platelet count increases toward the normal, though in these cases it may never reach normal even when the patient is apparently well. This fact is helpful in the recognition of these cases in the periods between attacks of purpura, the intermittent type of chronic purpura. Morphologically, the platelets show no characteristic abnormality; often they are larger than normal.

In typical cases of purpura hemorrhagica the other blood elements, as already explained, following the hemorrhages show the changes ordinarily found in post-hemorrhagic anemia. There is a moderate to marked fall in the red count depending on the blood loss; the cells show achromia and the color index tends to be low; there is slight variation in size and shape; some polychromatophilia and stippling occur; occasional normoblasts are seen; reticulated red cells appear in increased number when appropriate staining methods, as brilliant cresyl blue, are used, and these constitute one of the best evidences of bone marrow activity so far as red-cell formation is concerned. White cells are moderately increased, there being a moderate polynuclear leucocytosis, both relative and absolute; there is a slight relative lymphocytosis. These several changes in red and white cells vary in individual cases depending both on the stimulus to hyperplasia and the ability of the marrow to respond; response is less in those cases where toxic substances injure the bone marrow with respect to red and white cell forming elements, and on account of this we have a group of atypical cases.

Bleeding time is prolonged. Duke[13] noted that in purpura hemorrhagica bleeding from a small skin lesion was prolonged. Duke's method was to make a small incision in the ear lobe and at intervals of thirty seconds to blot up on absorbent paper the blood that had flowed. In normals such a hemorrhage stops in one to three minutes. Prolongation beyond ten minutes is distinctly abnormal. In purpura hemorrhagica the bleeding time may be from twenty minutes to several hours. The bleeding time serves as an index of the hemorrhagic tendency; when it is prolonged, platelet counts are low. According to Minot[1], a normal bleeding time occurs in purpura hemorrhagica only when the platelet count is above 60,000 per cubic millimeter. In similar fashion, bleeding time from vein puncture is prolonged in this condition.

Failure of retraction of the blood clot, as pointed out by Hayem, is another feature of the blood in purpura hemorrhagica. Normal blood when allowed to stand forms a firm, retracted clot and squeezes out a clear serum. In purpura hemorrhagica the clot is soft, jelly-like, and fails to squeeze out the serum in a normal way. This phenomenon is associated with the low platelet count and varies with variations in the platelet count.

Coagulation time varies but usually it is within normal limits. The various factors concerned in coagulation, fibrinogen, thrombin, antithrombin and prothrombin, vary within normal limits in most of the cases.

Clinical Features of Purpura Hemorrhagica

Cases of purpura hemorrhagica may be divided into acute and chronic; of the chronic type there are two sub-groups, continuous and intermittent purpura. Chronic purpura hemorrhagica has been particularly discussed by Bensaude and Rivet[14]. The chronic cases seem often to be confused with hemophilia, but the characteristics of the blood just enumerated for purpura hemorrhagica, in most instances, should distinguish them clearly from hemophilia. Sometimes, however, cases are seen intermediate in type between hemophilia and purpura hemorrhagica, and occasionally purpura hemorrhagica is hereditary. Cases may be further subdivided into primary or idiopathic and secondary or symptomatic purpura hemorrhagica.

Purpura hemorrhagica is most common in young adults. No large statistics are available for age incidence and other casuistic statements, since not enough of the reported cases distinguish between this disease with its characteristic blood picture and other forms of purpura.

Clinically this group of patients is characterized by hemorrhages into the skin and from the mucous membranes. Sometimes skin hemorrhages occur without bleeding from mucous membranes and vice versa. The amount and persistence of the hemorrhages vary. The skin lesion may be only a moderately diffuse purpura localized to certain body surfaces, as the legs, or it may be diffusely scattered over the body. The individual spots may be small or large. Frequently larger areas coalesce to produce hemorrhage into a wide area of skin surface. The individual purpuric spots show the changes in color of an ordinary traumatic bruise. Sometimes they are definitely elevated at their edges. Gravity has some influence on their occurrence. Recurrence on the legs when patients get up out of bed is noted often. At times they will be absent under a bandage and present on the unbandaged parts. The tourniquet sign shows the influence of the circulation in their production. At the periods when the hemorrhagic tendency is present a tourniquet applied for a short time (three minutes) tightly enough to cause venous stasis is followed by the appearance of small purpuric spots below its point of application.

Of bleeding from mucous membranes epistaxis is probably most common. Hematuria is frequent. Bleeding from gums, vagina, and gastro-intestinal tract are all observed. Hemoptysis is rare. Apart from the anemia and the unpleasantness, the hemorrhages do not cause symptoms. Occasionally, a cerebral hemorrhage will occur with ensuing hemiplegia. A rare retinal hemorrhage dims sight.

Following the bleeding, anemia develops and the patient has the pallor of a secondary anemia. The spleen as a rule is not palpable. The visceral manifestations are very few. Arthritis is uncommon. The circulation is affected by the anemia but shows no other changes. Fever is sometimes present, particularly in the severe cases. Terminal infections are common as might be expected.

Secondary or symptomatic purpura is a very common occurrence in association with a variety of chronic and acute diseases. Among chronic diseases, nephritis, cirrhosis of the liver, leucemia and neoplasm may be cited as conditions that frequently have an accompanying purpura generally late in the disease. In acute diseases purpura is also common particularly as purpuric rashes. In small-pox, scarlet fever and typhus, to cite but a few, purpuric rashes are often seen. The pathological physiology of purpura in many of these conditions is not thoroughly understood. In some, undoubtedly, the mechanism is the same as in idiopathic purpura hemorrhagica. In others there are no demonstrable blood changes similar to those in purpura hemorrhagica, and some other cause must be effective. Secondary purpura in vegetative or malignant endocarditis is common. Here the mechanism is different, at least in some of the cases, as it is dependent on the local action of bacterial emboli. Purpura occurs often in anemia apart from true aplastic anemia; however, in many of these cases the purpura is due to a terminal or temporary bone marrow exhaustion affecting platelet formation, and so its pathological physiology is the same as that for idiopathic purpura hemorrhagica and aplastic anemia already discussed.

Diagnosis

The term purpura hemorrhagica should be limited to those cases in which purpura and hemorrhages from mucous membranes occur accompanied by platelet deficiency, prolonged bleeding time and a non-retractile clot. In them other blood changes may or may not be found; the term secondary purpura hemorrhagica should be limited to those cases in which the characteristic blood changes are found as a sequence to various diseases causing the underlying bone marrow changes. Chronic intermittent purpura needs to be differentiated from hemophilia and occasionally it may be confused with bleeding from hereditary telangiectasis. The differences from these are pointed out in the chapter on hemophilia.

A purpura should always suggest the possibility of an underlying disease to which it is secondary. Search for evidences of such will prevent confusing a secondary purpura with an idiopathic one and save the diagnostic error of missing an important diseased condition. The frequency of early occurrence of purpura in both aplastic anemia and the leucemias should lead one to careful and repeated studies of the blood in all cases of purpura, not alone to recognize the blood changes of purpura, but those characteristic of anemia and leucemia.

Treatment of Purpura Hemorrhagica

The only effective means of controlling the hemorrhage is by transfusion. The platelets so introduced check hemorrhage as long as they persist. Transfusion may institute hyperplasia in the bone marrow and have a more prolonged or permanent effect. Repeated transfusions may tide over some temporary process causing platelet deficiency and so eventually lead to cure. This seems to be true in some cases the result of prolonged benzol poisoning. Local styptics help in some cases.

Transfusion is the best measure to use in dealing with the anemia and by counteracting the anemia transfusion brings about great improvement in the patient's general condition.

Between attacks and in the chronic and milder acute forms good hygiene, fresh air, and nutritious food are important. Drugs are of no service so far as the actual condition is concerned.

Purpura, Erythema and Allied Skin Disturbances and their Visceral Disturbances

Introduction

Certain skin lesions occur so often accompanied by manifestations of disturbance in internal structures as to justify regarding them as part of the expression of a general disturbance or general disease. At times evidences of these sub-dermal disturbances occur without any accompanying dermal lesion; at other times only the dermal change is in evidence. Variation in type of dermal change and alternation in association or non-association with visceral lesions happens often enough in individual cases to justify the belief that in these patients we are dealing with some general process and not with a local skin lesion. The entire character of the process in them indicates that its primary disturbance lies in some alteration either in the small blood vessels or in their content or in both. In one of these conditions, purpura hemorrhagica, just described, there are definite and characteristic blood changes; that is not true of the rest of the group.

These various facts, just enumerated, make it difficult to classify satisfactorily these disturbances and to determine in what connections they should be discussed. The blood changes in purpura hemorrhagica justify describing it under diseases of the blood. The vascular lesion, evident in all whether primary or secondary, indicates they might well be described under vascular lesions in association with vasomotor disturbances, Raynaud's disease, angeitis obliterans, etc. There is enough general disturbance to warrant their not being treated simply as skin diseases. Our ignorance as to their exact etiology and pathology prevents any thoroughly satisfactory grouping. There seems no very cogent reason for removing them from association with diseased conditions of the blood where they are discussed in many books, and hence they are here discussed in that connection.

As far as the skin lesions are concerned, there are many names as there are many surface appearances. Purpura simplex, Henoch's purpura, Schönlein's purpura, purpura rheumatica, peliosis rheumatica, erythema simplex, erythema multiforme, erythema multiforme bullosum, erythema multiforme vesiculosum, erythema iris, erythema urticans, erythema nodosum, erythema papulatum, erythema pustulosum, herpes iris, urticaria, urticaria pigmentosa and angioneurotic edema are some, though not all, of the names used by the dermatologist for a group of conditions which have in common focality and various combinations of dilatation and of exudation from small blood vessels, now of serum, now of red cells, now of white cells, but usually combinations of these various processes and with which frequently are associated visceral disturbances. It would seem to go too far to regard all of these as manifestations of a single process. Still as these various skin lesions do occur in association with certain general disturbances and as the exact form of skin lesion may vary from time to time in the same individual, it seems simpler to regard them as part of a general process rather than merely as local skin lesions, but we should not deny that the same skin manifestations may and often do appear as purely local skin processes. In this sense they may be discussed as a fairly definite clinical entity.

To Sir William Osler belongs the credit of grouping these conditions as a clinical entity. This he has done in various papers: On the Visceral Complications of Erythema Exudativum Multiforme[15]; Visceral Lesions of the Erythema Group[16]; On the Visceral Manifestations of the Erythema Group of Skin Diseases[17]; On the Surgical Importance of the Visceral Crises in the Erythema Group of Skin Diseases[18]; The Visceral Lesions of Purpura and Allied Conditions[19].

These titles emphasize what to him were very important phases of the subject. They seize upon erythema as the type or signal sign of the skin lesion; perhaps this is unfortunate, as hemorrhage or exudate seem to occur oftener than simple erythema. However, Osler was using merely a single term to imply the skin manifestations and it probably is unimportant which one out of the group was chosen.

Pathological Physiology

In purpura hemorrhagica the main cause of the hemorrhages was assigned to the platelet deficiency. A local vascular lesion of some sort could not be excluded; possibly the local change was merely trauma and the platelet deficiency caused the subsequent hemorrhage.

No such explanation will do, however, for the group at present under discussion. In the first place, there is no platelet deficiency. Platelet counts when made in these cases give normal values. Bleeding time is normal. There is no disturbance in any of the elements concerned in blood coagulation and coagulation time is normal. Studied by all means available the blood is normal both with respect to formed elements and with respect to plasma constituents. In the second place, there is no trauma.

The fault in this group seems to lie in the small blood vessels where there is some change increasing their permeability to various constituents of the blood, both serum and cells. This is a focal, not general, change. Microscopic examination reveals no demonstrable organic lesion.

Similar skin lesions appear after certain foods in those susceptible. Drug idiosyncrasy at times causes similar skin lesions. Serum sickness and certain anaphylactic changes bear resemblance to these changes. Toxic substances such as snake venom may produce some of these changes. These all suggest some change in the relation of vessel wall to its content as possibly concerned in the production of the lesions of the group of cases under discussion. Beyond this we have no justification in our knowledge for going.

Clinical Features

It has been rather the fashion to pick out certain cases with similar features and group them together as clinical entities. While this may help from the point of view of description, on the whole it brings confusion because this grouping has no basis in common causes and borderline cases are so numerous that the limits of the various groups become very vague. In fact, it is very difficult so to define these several groups to accord with the classification of the various text-books in general use. Purpura rheumatica, Schönlein's purpura, Henoch's purpura or purpura abdominalis are examples of clinical groupings very generally used but extremely difficult to delimit so that it is perfectly clear to the reader in which of these groups he should place a given case. Then in the same patient attacks will recur with much in them each time of a similar nature but with variation in skin lesion or visceral manifestation so as to overthrow completely the grouping to which the former attack was assigned.

It seems to me[20] that the subject is somewhat clarified by looking on all of these patients as having in common focal disturbances that allow of various types of exudation, giving skin lesions of different appearance, depending on the relative proportions of serum, red cells, white cells and tissue reaction, and visceral lesions of different sorts depending on the site and character of the visceral vascular lesion. This conception would explain the varying skin lesions, now with arthritis, now with abdominal pain, now with hematuria, etc., in all sorts of combinations.

Exudation of various sorts into the intestinal wall may occur. The appendix so distended produces the symptoms of appendicitis and may be removed at operation in the belief that an acute inflammatory process is present. The thickened intestinal wall interferes with peristalsis and constipation, colic, or intestinal obstruction result. Blood and serum escaping into the lumen leads to diarrhea, often bloody, or merely to intestinal hemorrhage, frequently severe. Similar changes in the stomach cause nausea and vomiting. Foci of hemorrhage occur in the kidney and result in hematuria. Albumin escapes and there is albuminuria. Edema of the kidney depresses renal function. Casts are found and it is extremely difficult to tell whether there is an acute nephritis or not. Blood may clot in the renal pelvis and in efforts to expel the clots, renal colic results simulating that from calculus. Serous exudate into joints causes arthralgia and often simulates arthritis. These changes may lead to actual tissue reactions producing chronic arthritis such as occurs in hemophilia. Uterine hemorrhage may simulate that of local disease such as hyperplastic endometritis, fibroid or cancer. These resemblances to various forms of disturbances which the surgeon deals with by operation become very important because so often mistakes are made in diagnosis and needless operations are performed. The group with the combination of purpura, arthritis and abdominal pain is frequent and is very generally spoken of as Henoch's purpura but even in the most typical cases in some attacks instead of purpura the skin lesions are of the erythema or urticarial type which renders unsatisfactory the term Henoch's purpura. Purpura rheumatica or Schönlein's purpura are still more unsatisfactory terms.

Some idea of the clinical picture is given by the following cases which have recently come under my own observation:

Case 1 (Peter Bent Brigham Hospital Med. No. 1016).—*Purpura, abdominal pain, blood in the stools.* A woman, aged forty-five, two weeks before admission, noticed red spots on the legs below the knee and then they appeared on the hands, forearms and lower abdomen. Those on the arms itched slightly. They varied in size from a pinhead to 0.5 cm. in diameter, at first bright red and then turning a darker red and gradually fading. On the day of admission a slight swelling which was red and quite tender appeared on the left instep, and two days later a slightly painful lump appeared in the middle of the forehead about 3 cm. in diameter which was raised about 0.5 cm. above the level of the forehead. At this time pain began to develop in her legs. The next day her left knee was painful on motion and her left ring finger was swollen at the second phalangeal joint. The left shoulder joint was tender on palpation. The patient had a very slight fever. A day or two later the patient had an attack of vomiting at night and the next day there was a new crop of skin lesions more papular than previously and more numerous on the face. The joint pains persisted for four to five days, varying in intensity. Two weeks after admission she complained of extreme pain in the lower portion of the abdomen. The abdomen was markedly distended, more or less rigid and was tympanitic throughout. The pulse became smaller, the heart sounds were weak, but she had no fever at this time. She was given several high enemas and the pain gradually disappeared, though the distention persisted somewhat longer. Two days later, however, the abdomen felt perfectly normal and the pain had entirely disappeared from the abdomen. A number of stools examined from the time of admission up to this period of abdominal pain showed strongly positive guaiac tests. Then the stools became negative for blood tests and thereafter for a period of nearly a month the guaiac tests were sometimes positive, sometimes negative. During this period the patient's condition greatly improved, and she left the hospital feeling comparatively well. During her stay in the hospital albumin was occasionally found in her urine and an occasional cast was seen, but there was no hematuria.

Case 2 (P. B. B. H. Med. No. 1143).—*Purpura, abdominal pain, pain and swelling of the ankles, hematuria.* A boy, aged thirteen, about six weeks before admission, was suddenly seized with sharp cramp-like pain in the abdomen, more severe about the region of the umbilicus. This pain did not radiate and it lasted for about ten minutes. Since then there have been many recurrences of similar paroxysms of abdominal pain and he has never been free from the sensation of discomfort in the abdomen during this time. When the pain is severe he occasionally vomits a small amount. This vomiting is not preceded by any nausea. The first two urine specimens examined in the hospital showed numerous red blood cells, subsequently none were found. The patient was distinctly emaciated; his abdomen had a doughy feel. Bismuth Roentgen-ray studies of his gastrointestinal tract showed distinct irregularities in the pyloric and prepyloric region. The stomach emptied rather slowly. When the bismuth reached the small intestine the loops looked wide and atonic. While in the hospital the patient frequently had attacks of very intense abdominal pain which would double him up and sometimes he would vomit. At times food taken several hours previously was found in the vomitus. Ten days after the first bismuth Roentgen-ray examination a repetition showed again irregularity in the prepyloric region with a slow emptying time for the stomach. After two weeks' stay in the hospital the patient began to improve, his colic-like pains decreased, his appetite improved and he looked very much better. After nearly a month in the hospital there was a recurrence of pain in the abdomen, followed the next day by pain and swelling in the right ankle. A day later several purpuric spots appeared on the legs. These gradually faded away not to recur. During the latter part of his stay in the hospital a small amount of blood reappeared in the urine and albumin was present with an occasional cast.

Case 3 (P. B. B. H. Med. No. 1069).—*Purpura, diarrhea, blood in the stools, abdominal pain, painful swollen joints.*—Three and one-half weeks before the patient, a girl, aged eleven, came to the hospital, a rash appeared on the back of the calves and over her lower legs which gradually went up the legs and a few appeared on the trunk. Finally a rash appeared on her face. The rash was red in color and consisted of discrete, sharply defined macules. During the first three days after the rash appeared, the patient vomited frequently yellow greenish material, free from visible blood. During this time her stools were dark colored. One week after the rash appeared, her ankles became swollen, and two days later swelling appeared in her hands. This swelling in the hands and feet disappeared but recurred again later. When the patient came to the hospital there was slight abdominal tenderness, there was a marked macular and papular rash over the legs, feet and arms, in places dark red, in other places paler, purplish or yellow in color. On one ankle there was a bleb about the size of a dime. At this time there was no obvious involvement of any joint. After two days in the hospital the patient had a stool in which there was bright red blood and a little later she involuntarily passed about four c.c. of blood. The next day there was diarrhea with several watery stools, most of which showed blood. On this day the right hand and arm as high as the elbow were distinctly swollen, but not very tender. Several days later there was a recurrence of the diarrhea, there being very numerous stools most of which contained blood. This persisted for several days and then diarrhea gradually decreased, though positive guaiac tests continued to be obtained in her stools for a long time. After being in the hospital for a month, a new crop of purpuric spots appeared on her feet. Four days later a new crop came on her legs. A week later she again had pain in her abdomen and vomited. Shortly afterward she passed a large tarry stool. She remained in the hospital for nearly four months with frequent recurrences of what has already been outlined and then left in good condition. She was seen a year later and reported that she had had a few purpuric spots in the interval but no recurrence of the diarrhea and abdominal pain.

Case 4 (P. B. B. H. Med. No. 3599).—*Purpura, painful joints, hematuria.* A man, aged twenty-five, about two weeks before admission, developed a sore throat. Five days ago his knees became a little painful on motion and after resting would feel stiff. For two days his feet have been a little swollen. Nine days ago his feet became tender and were painful when he walked about. On yesterday he had a little trouble pulling on his boots and later in the day noticed that there was a red rash about his ankles. When he came into the hospital, on both ankles and over the calves of both legs there were many dark red, hemorrhagic areas from 0.5 to 8 mm. in size. A few of these were covered with fine crusts. Both tonsils were enlarged, red and slightly ragged. The urine contained a moderate amount of albumin, and numerous hyaline and granular casts. A specimen passed nearly two weeks after admission was smoky and contained many red blood cells. This was at a time when the throat had cleared up and the purpura had disappeared. After about three weeks in the hospital and when the patient had been up out of bed for three days, purpura returned over the ankles with slight pain and swelling in the ankles. The blood was very slight in amount in his urine at this time but ten days later became more abundant. This patient had a positive Wassermann reaction and there was an ulceration in his palate. Renal function was slightly impaired as shown by the blood urea nitrogen which was 25 mgm. per 100 c.c. of blood, with an index of urea excretion according to McLean's formula of 40.5 per cent. Some time later the blood urea nitrogen was 21 mgm. with an index of urea excretion of 49 per cent. The phenolsulphonephthalein test at about this time gave an excretion in two observations of 67 per cent. and 50 per cent. respectively and the urine always contained a considerable amount of albumin and numerous casts, hyaline and granular in character, so that the diagnosis of acute nephritis was also made, though this may have been incorrect.

Case 5 (P. B. B. H. Med. No. 5372).—*Erythema nodosum, abdominal pain, vomiting, slight diarrhea.* A woman, aged twenty-seven, for about four weeks had had grumbling pains in the left upper quadrant of the abdomen. On two occasions she vomited and for several periods of about a week there was slight diarrhea. Nothing abnormal was noted about the vomitus; no blood was observed in the stools. A few days ago the patient felt rather chilly and went to bed. The following morning after walking down stairs she noticed soreness in both legs from the knee to the ankle. That night she noticed what she called "mosquito-bite like" areas over both lower legs. Two mornings ago these seemed to be fading but by today had become larger and felt lumpy. During this period there has been slight sore throat. When she came to the hospital there were numerous discrete lesions over both legs. These lesions were slightly raised, reddish-blue, or slightly yellow in color, with ill-defined edges, measuring from 1 to 4 cm. in diameter. On palpation they give a distinctly nodular feel. On pressure most of the color disappears from the lesions. When she came in there was slight fever which quickly disappeared. All the gastrointestinal symptoms likewise disappeared. Her urine examination was normal.

Case 6 (P. B. B. H. Med. No. 5543).—*Erythema multiforme bullosum, gastric disturbance.* A boy, aged thirteen, for the past five years every August has had a gastric upset with an erythema on the right side of his lower jaw. This usually lasts five to six days. Eating strawberries often produces a little urticaria and on one occasion he had urticaria from eating fish. About a month ago the same appearance as usual occurred on his jaw. Then red spots appeared on his legs and arms. Soon a blister would form over these red spots which would break in about twenty-four hours, leaving a red area with a little black speck in the center. About five days ago blisters appeared in the mucous membrane of his mouth. On admission he showed over the mid-portion of his right lower jaw an irregular area of yellow crusts. Irregularly scattered over the arms and legs there are small areas of erythema with blackish brown spots in their centers. Over the back of his thighs there are a number of red areas, some almost entirely covered with blebs containing a serous fluid. The edges of these areas are sharply demarcated. Over the palms of the hands and the soles of the feet are a large number of blebs varying in size from a ten-cent piece to a twenty-five-cent piece. When the blebs break it is seen that the lesion as far as ulceration is concerned is very superficial. On the lips there are similar blebs, and apparently they have occurred also on the gums, appearing here as erythematous areas slightly ulcerated. These lesions rapidly cleared during about ten days' stay in the hospital. The patient's urine was normal and there was no blood in the stools.

Case 7 (P. B. B. H. Med. No. 5661).—*Erythema multiforme vesiculosum, abdominal pain.* Eleven days before admission, n a woman, aged twenty-nine, generalized pain in the abdomen developed. This began in the morning and got worse in the afternoon. During the night it was severe enough to prevent sleep. Her local physician saw her the next day and diagnosed the condition as salpingitis. He prescribed a vaginal douche and after a few days the pain subsided. Then the pain recurred and she went to a dispensary where she was diagnosed as having gallstones. With this attack she vomited and continued to vomit until she was sent to the hospital where she was first admitted on the surgical side. There it was found that she had an irregular, blotchy, erythematous eruption over her face and almost the entire body. These erythematous areas did not seem to be elevated and they faded on pressure. The abdomen showed generalized tenderness. Her feet and ankles were swollen and tender. In twenty-four hours the skin rash had largely disappeared, leaving a slight puffiness of the face, hands and feet. The rash reappeared and a week later a different type of rash appeared on the arms and legs, consisting of small, irregular, dusky red areas, 2 to 6 mm. in diameter, which did not disappear on pressure. On the tops of many of these lesions small vesicles appeared which subsequently became slightly pustular. The patient now complained of abdominal tenderness and there was slight diarrhea. The urine showed a slight amount of albumin, numerous casts and a 'phthalein output of fifteen per cent. in two hours, which in two or three days had increased to twenty-four per cent., and a week later to thirty-four per cent. The patient had a moderate degree of irregular fever. At times the pain in her elbow and wrists became more severe and kept her awake. After being in the hospital for nearly a month, she had a recurrence of the pain in her abdomen and her left arm from the elbow to the shoulder became swollen, tender, and felt hot, but it was not red. This swelling gradually subsided and the tenderness disappeared. From time to time the patient had a severe headache. She gradually improved and left the hospital feeling quite well after a stay of about two months. Before she left her 'phthalein excretion had risen to fifty-five per cent.

Case 8 (P. B. B. H. Med. No. 5908).—*Urticaria, intestinal obstruction.* The patient, a man, aged fifty-eight, had had a large number of attacks of localized swelling in the right hand and other manifestations of urticaria. On the day before coming to the hospital, he was in his usual health until the afternoon. While having tea his abdomen became distended, there was some belching of gas, he felt rather uncomfortable and went to bed. He began to have pain in his abdomen chiefly in the epigastrium and along the right costovertebral angle. His abdomen was generally distended. There was a fair bowel movement about 9 p. m. Later an enema was given and returned with very little fecal material. The distention and discomfort continued so that he slept poorly. The next morning, January 7, he came to the hospital, and his abdomen was found to be distended and diffusely painful and slightly tender. The abdomen and the character of the pain suggested distinctly intestinal obstruction. For twenty-four hours very little result was obtained from enemas or rectal tube. Then a good fecal result was obtained and the patient passed a considerable amount of gas. Forty-eight hours after admission his abdomen was much less distended and the patient was much more comfortable. Four days after admission scattered patches of erythema and edema appeared over his hands, arms and feet, which he said were similar to those that he had had repeatedly after eating fish, shellfish, or canned goods that were possibly not quite good. He recalls having eaten sardines on the day that his abdominal distention and discomfort developed. These findings suggested that possibly the intestinal obstruction was due to a similar type of lesion in the intestinal wall and on the next day, January 12, bismuth Roentgen-rays of his gastro-intestinal tract showed, five hours after the taking of the bismuth meal, in one of the upper loops of the ileum a dilatation producing a sausage-shaped shadow, the distal end of which was narrow. After this all symptoms of intestinal obstruction disappeared, a repetition of the Roentgen-ray study three days later showed no signs of a dilated loop and a repetition ten days later again gave no evidence of obstruction.

Case 9 (P. B. B. H. Med. No. 5823).—*Purpura, arthritis, abdominal pain, hematuria, blood in the stools.* A man, aged twenty, six years ago had an attack of rheumatism in which both knees were slightly swollen and quite painful, particularly at night. Since then he has had a similar attack about once a year. About nine weeks ago another attack of rheumatism developed in which his right knee became sore. A little bit later his left knee became very painful and slightly swollen. The right knee cleared up but the left knee continued and is still swollen and painful. For a year the patient has had an ulcerated tooth in the right lower jaw with a swelling nearby from which pus exudes on pressure. Six days before he came to the hospital, he began to have a sensation of pressure in the epigastrium, giving him enough distress to keep him awake during the night. He raises a good deal of gas. Four days ago he began to have hiccups and to vomit about once or twice an hour. There was very little nausea. The vomitus was bitter, greenish in color, and never contained anything like blood. On admission, numerous small purpuric spots were found over both elbows and over the lower part of the sacrum, which he says had been present for three to four days. A carious tooth was found as described. The left knee was somewhat larger than the right, somewhat painful, not hot, and did not appear to contain fluid. His left leg was slightly flexed at the knee and held in that position. He had a moderate fever. During his first few days in the hospital, the urine contained a very slight amount of albumin with a few hyaline casts. The 'phthalein elimination was forty-two per cent. in two hours. In his stools a strongly positive benzidin test for blood was found. The pain in his knee decreased and then after four to five days increased and at this time there appeared on the forearms, wrists, legs, ankles and feet many small, slightly indurated, erythematous plaques, definitely elevated and about 1 cm. in diameter. These gradually disappeared and a week after this crop had come out, the patient's temperature suddenly rose to 102°F., and there was marked swelling of the left knee and a reappearance of purpuric spots on the forearms, ankles and feet. Now there were definite signs of fluid in the knee joint. The patient was unable to flex his knee on account of pain. At this time the bad tooth was extracted and pus was found about its root. For the next two weeks the temperature ranged between 99° and 100°F. Then it rose again to 102.5°F. with a fresh crop of purpuric spots on the forearms, ankles, and feet. The patient had begun to cough up a considerable amount of blood. During this time a small amount of blood had appeared in his urine and the casts had increased in number. Shortly after this last group of purpuric spots appeared, the urine became definitely hemorrhagic in type and thereafter contained practically always a considerable amount of blood, though different specimens might show more or less blood. A guinea pig inoculated with urinary sediment was negative for tuberculosis. After a month's stay in the hospital, the patient had a definite secondary anemia, but he had been free from purpuric attacks for some little time, blood in his stools was no longer found and the blood in his urine had somewhat decreased. Roentgen-ray examination of his knee shortly after this showed bony enlargement and slight irregularity but no evidence of a destructive process. Now the patient's temperature became a maintained temperature first around 101°F. and then increasing to 102°F. and finally rising to about 103°F. with a gradually increasing pulse rate. During this period the left knee continued swollen and painful, with some variations up and down in the activity of the process. After about two and one-half months' stay in the hospital with this continued fever, continued hematuria and continued activity of the process in the left knee, definite signs were made out of a pulmonary process and tubercle bacilli were isolated from the sputum in small numbers. A month prior to this, sputum examinations had shown no tubercle bacilli. A Roentgen-ray plate of the chest showed changes suggesting a diffuse miliary tuberculosis with, in places, conglomerate tuberculosis. There were no further crops of purpura and the patient died about three and one-half months after admission. At necropsy there was an acute miliary and conglomerate tuberculosis of the lungs with areas of caseous pneumonia, apparently an active and recent tuberculous process. The kidneys were slightly enlarged and showed small foci of hemorrhage. On microscopic examination of the kidneys there was no nephritis but possibly a slight degenerative change in the tubular epithelium with numerous foci of intertubular and intratubular hemorrhage explaining the persistent hematuria. No tuberculous lesions were found in any of the abdominal viscera. The gastrointestinal tract seemed to be normal. The stools for a period of three months before death gave no test for blood.

Diagnosis

The association of a history of skin lesion with visceral symptoms, the search for skin manifestations when the visceral crises are prominent, the remembering that visceral manifestations may precede skin lesion and are to be thought of when fever is absent and the visceral symptoms have no obvious cause, are the means of preventing errors in diagnosis, errors which at times lead to unneeded and unavailing operations. At best errors in diagnosis will occur. The absence or slight degree of fever, the absent or slight leucocytosis usually present in this group aid in distinguishing the symptoms from those caused by inflammatory processes.

Prognosis

In this group prognosis is very uncertain. Many cases have repetitions of the symptoms, sometimes over a long period of years. Individual attacks usually are from one to six weeks in duration with remissions and exacerbations of some or all of the symptoms and changes. The condition is rarely fatal unless complications such as tuberculosis or nephritis develop. There is no way of judging when seen in the first attack, whether there will be recurrences or not.

Treatment

There is no specific treatment. General hygienic methods to build up the patient's general condition are indicated. Skin tests for protein sensitivity may explain an occasional case and give the proper therapeutic hint. I am extremely skeptical of the value of the much used calcium chloride or lactate. It can do no harm and so may be tried. In cases with an urticarial basis 1 c.c. of adrenalin subcutaneously may be very effective. Salicylates, aromatic sulphuric acid, oil of turpentine, and ergot are advised; just why I cannot see. It seems wiser to me to give nothing than to try such improbable measures.

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CHAPTER XX

HEMOPHILIA

By JAY McLEAN

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Synonyms.—Hemorrhagic diathesis, idiosyncrasia hemorrhagica, hematophilia, amychemorrhagica, morbus haematicus, Bluterkrankheit, Blutsucht, hemophile, hemorrhagie constitutionelle.

Definition.—Hemophilia is an hereditary abnormality of the blood or blood forming organs, limited to males, but transmitted only by females, and characterized by a deficiency of prothrombin in the blood, which condition effects a delayed coagulation time and a liability to immoderate or fatal hemorrhage.

HISTORY

N. Rothschild[1] has come to the conclusion that hemophilia must have been known to the ancient Jews for there are certain dispensations in the Talmud with regard to circumcision, namely: (1) A boy must not be circumcised if two sons of his maternal aunts have died from the operation. (2) A boy must not be circumcised if his two brothers by the same mother, but by different fathers, have died from the operation. Rabbi Simon ben Gamaliel ordered that the son of one of four sisters should not be circumcised for previously the sons of the three other sisters had died after the operation. As Rabbi Simon ben Gamaliel lived in the second century A. D., it is claimed that this is the oldest reference to the disease.

Among medical writings according to the researches of Bulloch and Fildes[2] the first mention of a disease resembling hemophilia in any way is found in those of Khalaf ibn Abbas, Abu-al-Kasim, commonly called Albucasis, the greatest surgical writer of the Moorish period. Albucasis states that in a certain village there were men who, when wounded or bled, suffered an uncontrollable hemorrhage which caused death. The same fate resulted to the boys if their gums were rubbed harshly.

In 1793 an anonymous author, presumably G. W. Consbruch, editor of the *Medinische Ephemeriden*, the publication in which the reference appeared, described a classical instance of the disorder which is the first in the literature of hemophilia. Another genuine case was published by Rave[3] in 1796.

Knowledge of the existence of the disease did not become general until after the publication in 1803 by Dr. John C. Otto[4], a physician of Philadelphia, of "An account of the hemorrhagic disposition existing in certain families" in which he describes the occurrence of the condition in the male descendants of a woman named Smith, who had settled seventy or eighty years previously in the vicinity of Plymouth, New Hampshire. Otto stated that: "Males only are affected and all are not liable to it. Though females are free they are capable of transmitting it to their children." This paper attracted much attention in both America and Europe, and stimulated the publication of many genuine cases. In 1820 Nasse[5] stated what has become known as his law (although previous writers had emphasized the facts) namely that: "Males alone are the subjects of hemophilia and that the disease is transmitted by normal females through their marriage with normal males."

The most important publications since Nasse's work dealing with the disorder in a systematic manner have been the two editions of Grandidier's monograph (1855 and 1877), the monograph of Wickham Legg (1872), the article by Immermann (1876) and the thorough critical work of Bulloch and Fildes (1911).

The history of the progress of our knowledge of hemophilia may be conveniently divided into two periods, which are: (1) that period extending from the earliest mention of the disease to the time when the coagulation of the blood became a subject of scientific investigation, and (2) the period since, inaugurated by the publication of Alexander Schmidt's researches, in which the various factors concerned in the phenomenon of the coagulation of the blood have been studied individually and in their relation to the train of events resulting in the solid clot.

The literature of the first period was confined largely to the recording of bleeding conditions (many of which were not true hemophilia), to the gathering of pedigrees of hemophilic families, to the description of the symptoms exhibited, to unsuccessful attempts toward locating a characteristic pathologic lesion at autopsy, and to the empirical treatment of the condition.

In the second period we find recorded the work on the coagulation of the blood itself. The first result of this work was the establishment by Wright[6] in 1893 of the fact that hemophilic blood exhibits a delayed coagulation time.

The most fruitful work concerning the nature of this retardation of the clotting is that of Addis[7] 1911, of Howell[8] 1914, and of Minot and Lee[9] 1916, who have shown that the retarded coagulation is due to an inadequate amount of prothrombin in the blood.

SYMPTOMS

The cardinal symptom of hemophilia is a chronic tendency in males to prolonged internal or external hemorrhage. The bleeding is characterized by its persistent oozing nature. The condition invariably presents itself in early childhood, indeed usually in the first year of life, although the umbilicus at birth is rarely a site of hemorrhage. Hemophilia in the child is often first revealed by a simple operation as the snipping of the frenum of the tongue or of circumcision, or by hemorrhage from the mouth following the cutting of the milk teeth and during the eruption of the permanent teeth. The most frequent sites of the hemorrhage are the broken skin, the mucous membranes, the subcutaneous tissue and the muscles and joints, although hemorrhages do occur into the body cavities and from the internal organs.

It has been noted that this chronic tendency to bleed is variable in intensity, and this is in accord with the finding that the blood of hemophilics has a fluctuating coagulation time, at times approaching closely that of normal blood. A slight trauma at one time may result in a severe hemorrhage whereas the same degree of trauma received at another time may cause no hemorrhage. While it has been repeatedly recorded that hemorrhages may arise spontaneously, often occurring while the subject sleeps, the onset of the symptoms usually follows some injury, either slight or violent, received in the course of play or otherwise. Falls frequently result in hematomas which may be of large size and extend for a considerable distance from the origin of the bleeding. The persistent oozing may last for hours, days or weeks. Clots may form but they do not do so in the wound and thus they are not in a location to adequately seal the wound and arrest the hemorrhage. The bleeding may continue until a state of profound anemia is brought about, in which the flowing blood will hardly stain the bandages or bed linen. The hemorrhage may continue until the patient dies, or as is more often the case, until an increased coagulability of the blood occurs with cessation of the bleeding followed by surprisingly rapid regeneration of blood and recovery of the patient. While external hemorrhages are accompanied by no constitutional symptoms unless the loss of blood is excessive, internal hemorrhages such as hematomas, intramuscular hemorrhages and joint effusions may cause considerable pain, a rise in temperature and malaise. The hemorrhages are usually single and of fair size and the resultant play of colors appearing shortly after subcutaneous and joint hemorrhages should not be confused with the multiple skin blotches of hemorrhagic purpura.

Bleeding does not occur in the course of skin scarification for vaccination, nor in simple pricking of the skin to secure a drop of blood. Venepuncture if skillfully executed is without danger.

Joint Affections

Hemorrhages into the joint cavities and the bones forming the joints are extremely common. These are said to occur spontaneously, but many hold the view that they arise only following some trauma to the joint. The knee and elbow joints are most often involved. The bleeding takes place from the synovial membrane into the capsule, or there may be only hemorrhages into the diaphysis or the epiphysis entirely behind the articular surface. In bleedings into the joint capsule, König[10] recognized three stages of insult, *viz.*: hemarthrosis, panarthrosis, and deformity.

A hemarthrosis may be rapidly or slowly absorbed, leaving the patient without any organic or functional defect. In fact, hemorrhages may occur frequently in the same or other joints and be absorbed quite promptly and completely without a remaining defect. Gocht[11] has observed forty-five hemorrhages into the right knee which were absorbed without producing pathological changes in the anatomy of the joint. The left knee of the same patient suffered inflammation and was contracted only after thirty-nine well borne hemorrhages.

However, hemophilics are not usually so fortunate for the presence of blood in the joint may lead to bone destruction. The synovial membrane loses its glistening smooth surface and may hypertrophy and also become gouged out in a few or many places, the cavities extending from the articular surface into the epiphysis as though bitten out with rongeur forceps (Baetjer). Also the blood may organize with calcium deposition in it affecting limitation of motion and there may be ankylosis.

There has been at times some confusion in deciding whether a swollen joint is affected with tuberculosis or hemophilic hemorrhage. Indeed, surgeons of renown have incised hemarthroses under the impression that they were tuberculous. The diagnosis should not be in doubt if the following points are kept in mind:

Tuberculous Joint	*Hemophilic Joint*
1. There is usually atrophy of the muscles above and below the joint.	1. No atrophy above or below the joint.
2. There is a local rise of temperature at joint.	2. No local rise of temperature.

3. There is a further localized area of temperature.	3. No localized area of temperature.
4. Only one joint is usually affected.	4. Usually but one joint is involved at any one time, although eventually many joints may suffer.
5. Not recurrent.	5. Many recurrences.
6. Tuberculin reaction positive.	6. Tuberculin reaction negative.
7. No subcutaneous discoloration.	7. Discoloration present.
8. Onset very slow.	8. Onset sudden.

X-RAY EXAMINATION

Active Tuberculous Joint	*Hemophilic Joint*
1. Cloudy or hazy due to hypertrophy of articular membrane.	1. Clear.
2. Shows destruction of the articular surfaces starting from the periphery and working toward the center resulting in peeling off of the articular surface.	2. The destruction is of two types: (i) As though a rongeur had bitten through the articular surface into the epiphysis. These cavities may vary in diameter from four to twenty millimeters; (ii) hemorrhages occurring in the epiphysis resulting in bone absorption and leaving characteristic clear punched out areas, the articular surfaces being intact.
	3. While there is fluid present in an active tuberculous joint it does not undergo organization, whereas the blood present in a hemophilic joint may undergo calcium organization which then exhibits a characteristic picture.

An old tuberculous joint may present punched out areas in the articular surface and underlying epiphysis as in the first mentioned type of hemophilic joint lesions, but it never has these combined with the clearly punched out areas entirely within the epiphysis behind the articular surface.

Probably few hemophilics escape articular deformity of some degree although the frequency of hemorrhages into the joints becomes less as the man grows older.

ETIOLOGY

We do not know how the abnormal condition of hemophilics originated, but once started the disorder is transmitted through generation after generation by the female descendants, although it is manifested only in their male issue. In the literature one finds many reports of hemophilia occurring in women. All of these reported cases up to 1911 were examined in detail by Bulloch and Fildes[2]. In their precise review of over 900 writings on hemophilia they found in forty-four families, sufficiently well described to be of conclusive value, only ten which claimed to contain female bleeders. The bleeding in these cases was from sites not uncommon in women, namely from the uterus (postpartum hemorrhage), from rupture of the hymen during coitus, from gastric ulcers, from the teeth, and from bleeding associated with menstrual disorders. They conclude: "Thus in none of the families of bleeders which have been comparatively well described and recorded in some detail do we find unequivocal evidence of abnormality in women, that is to say, any abnormality beyond what might be expected in connection with females taken at random. That the females in bleeder families are abnormal, in some unknown particular must be readily admitted. They are the active propagators of the disease. But if the abnormality is so slight or entirely latent as Immermann has suggested, further discussion of the subject will be without profit until some method of diagnosis has been devised which does not depend on the outward symptoms." Such a method has been devised by Howell[8]. When a sufficient number of cases have been examined by this method, that is, the determination of the prothrombin time the question should be settled with finality.

Statistics show that women of bleeder stock are unusually fertile. According to Wachsmach's figures 114 children were born in 12 families yielding an average of 9.5 children per family. In Bulloch and Fildes' collection of genuine cases the average number of children per family was 6.1 which is still considerably above the average. Lossen points out striking instances of such fertility in the Mampel family. This pedigree shows 4 families with 19 children, 2 with 13 children each, 2 with 11 children each and several with 10, 9 and 8 children each.

The sex ratio in hemophilic stocks shows great abnormalities. In the 44 families mentioned above there were 644 males, 464 females and 56 individuals whose sex is not stated. Even assuming that all of the 56 individuals whose sex was not stated were females there still exists an unheard of ratio of males to females, *viz.:* 1,246:1,000. Between the years 1838 and 1908 the Registrar-General for England and Wales gives the ratio of males to females as 1,041:1,000. It would appear that the conductors of the disease tend to produce an excess of males.

Girls of hemophilic stock who have sons do not all necessarily transmit the disorder. In Bulloch and Fildes' collection of 44 families, of 125 mothers who had sons, 37 (twenty-nine per cent.) escaped having bleeders. In the Mampel stock there were 8 mothers out of a total of 28 (twenty-seven per cent.) who did not transmit the abnormality. Nor are all sons of a conductor subject to the disease. In one bleeder stock only 37 sons out of a total of 82 sons of mothers who transmitted the disease were bleeders.

Cases of hemophilia in which no inheritance was demonstrated have been reported from time to time but they are regarded by Bulloch and Fildes, who are particularly interested in the hereditary aspects of hemophilia, as instances of the classical disease in which the ancestors and especially the collaterals have not been thoroughly searched for conductors. Nevertheless, they present one genealogy worked out by Gettings in which he was unable to find any instance of the disease among the collaterals although these were inquired into through a number of generations. Addis[12] and others caution against the definite conclusion that "de novo" cases may not arise.

There are no authentic records of the direct transmission of the disease by males. In the Bulloch and Fildes' residue of genuine cases, the eleven instances, in which it is claimed that the condition was propagated by the male, are explained by them in this manner. Intermarriage has been common, especially among the geographically isolated hemophilic families, so that a woman supposedly normal, but in reality a conductor, may marry a man in a bleeder family and transmit the disease to his sons.

Hemophilia is apparently a sex linked character. The facts known about the transmission and occurrence of the disorder are explained by this theory. According to this theory, two kinds of spermatozoa are produced, one with a characteristic odd chromosome, known as the sex or x-chromosome, and one in which this chromosome is lacking. The ova on the contrary all possess an x-chromosome. When the ovum is fertilized by a spermatozoon lacking the x-chromosome, the resulting zygote has only one x-chromosome and develops into a male. On the other hand if the ovum is fertilized by a spermatozoon possessing the x-chromosome, the resulting zygote has two x-chromosomes and develops into a female. If we indicate hemophilia (H) as linked to the single male x-chromosome the results of fertilization may be expressed, in accordance with the Mendelian principles, as follows:

	Male, hemophilic			Female, normal	
	$X\text{-}H\ O$			$X\ X$	
Spermatozoa	$\frac{X\text{-}H}{1}$	$\frac{O}{2}$	Ova	$\frac{X}{3}$	$\frac{X}{4}$

The combination of 1 and 3 will produce a female conductor; the unlinked x-chromosome is assumed to counteract the influence of the hemophilic linked x-chromosome so that this individual does not manifest the disease.

The combination of 1 and 4 will also produce a female conductor.

The combination of 2 and 3, and 2 and 4 will produce normal males.

If the normal male marries a female conductor we will have the following results:

	Male, normal	Female, conductor
	$X\ O$	$X\text{-}H\ X$
Spermatozoa / Ova	Spermatozoa $\frac{X}{1}$ $\frac{O}{2}$	Ova $\frac{X\text{-}H}{3}$ $\frac{X}{4}$

The combination of 1 and 3 will produce a female conductor.
The combination of 1 and 4 will produce a female normal.
The combination of 2 and 3 will produce a male hemophilic.
The combination of 2 and 4 will produce a male normal.

While there is still some question about the occurrence of hemophilia in the female, it would be possible to have a female hemophilic, if a male hemophilic should marry a conductor. The results in this event would be:

	Male, normal	Female, conductor
	$X\text{-}H\ O$	$X\text{-}H\ X$
Spermatozoa / Ova	Spermatozoa $\frac{X\text{-}H}{1}$ $\frac{O}{2}$	Ova $\frac{X\text{-}H}{3}$ $\frac{X}{4}$

The combination of 1 and 3 will produce a female hemophilic manifesting the disorder for there is no counteracting unlinked x-chromosome.
The combination of 1 and 4 will produce a female conductor.
The combination of 2 and 3 will produce a male hemophilic.
The combination of 2 and 4 will produce a male normal.

The bulk of genuine cases of hemophilia has been reported from Germany, Switzerland, England and the United States. In the little Alpine hamlet of Tenna the disease has existed through six or seven generations.

PATHOLOGY

At section no characteristic gross or microscopic lesions are found except in joints which have suffered deformity following hemorrhage into them. In 1893–1894 A. E. Wright demonstrated that there was a defect in the blood causing a retardation of the clotting time. He was also the first to point out the "hemorrhagic increase in the blood coagulability" following immoderate hemorrhage. Blood tested at this time may coagulate as promptly, or nearly as promptly, as normal blood. Addis[12] has reported that the blood coagulation time may vary from day to day in the interhemorrhagic periods as much as thirty-eight to eighty minutes in one patient and from fifty to ninety minutes in another patient. The work of Arthus and Pages demonstrated that the presence of calcium ions is necessary to initiate the first stage of the coagulation of the blood, namely, the reaction resulting in the formation of thrombin from prothrombin. Wright observed a craving for calcium in certain of his hemophilic patients, and he thought that in this condition there was a deficiency of calcium in the blood. Recent work has not generally confirmed this view, although Hess has lately reported a case of classical hemophilia in which there was a deficiency in the calcium of the blood. Morawitz and Lossen[13] and Sahli[14] believe that the fundamental defect lies in an inadequate amount of thrombokinase (cephalin or thromboplastin) not only in the corpuscles but in the tissues in general and Nolf[15] shares this view. However, they present no facts supporting this general view, but Minot and Lee[9] have shown that hemophilic platelets are not as available for their role of initiating coagulation as normal platelets. As platelets are normally a source of cephalin there is this much ground for stating that the amount of thromboplastic material liberated and available for the purpose of accelerating the formation of the clot is reduced below normal. The tissues at large contain, as far as we can estimate, a normal amount of thromboplastic substance. Howell[8] has shown that if the tissue juice (containing the cephalin) be admixed with the hemophilic blood, through faulty technique in securing the specimen, the coagulation time may be reduced to normal.

Addis[7] traced the cause for the retarded coagulation to the prothrombin factor and from his careful experiments he concluded that in hemophilia there exists a qualitative defect in the prothrombin. Howell[8] also locates the fault in this factor, but he has demonstrated that there is an actual deficiency in the amount of prothrombin available. Howell isolated prothrombin from hemophilic blood and found that the prothrombin exhibits no qualitative defects as judged by its interaction with fibrinogen, in the presence of calcium chloride, to form fibrin. The clot formed in twenty minutes in the specimen of hemophilic blood, while the control of prothrombin from normal blood required practically the same length of time, *viz*,: twenty-eight minutes. Howell concludes that the delayed coagulation of hemophilic blood is due to a subnormal amount of prothrombin in the circulating blood and that as the antithrombin has been found to be present in normal or slightly supranormal amounts, resulting in a relative increase of this factor, the delay in the coagulation of the shed blood is easily explained. So far as we know the prothrombin present in blood plasma is furnished by the blood platelets and Howell thought the ultimate cause might be found in them. Minot and Lee[9] have clearly proven that platelets of hemophilic blood though present in normal numbers are only slowly available for their normal function. They added platelets of hemophilic blood to normal plasma and controlled this with a specimen of the same normal plasma to which were added normal platelets. The platelets from the hemophilic blood with the normal plasma showed a delayed clotting time. The clotting time of a mixture of hemophilic platelets and hemophilic plasma in any concentration of platelets was always longer than that of a mixture of normal platelets and hemophilic plasma. Fonio[16] also maintains that in this condition the platelets are fixed and unavailable for their normal function. This unavailability of the platelets is, as pointed out before, a double loss for not only the prothrombin content but also the cephalin of the platelets is less available. This delayed functioning on the part of the platelets is offered by Minot and Deny in explanation of the phenomenon of reclotting of hemophilic blood. If the first clot which forms is removed the remaining serum will clot; in the time following the removal of the first clot more prothrombin has become available.

The fibrinogen is present in normal amounts in hemophilic blood; there is no variation in the hydrogen ion concentration, nor have the serum albumin, serum globulin or total protein been shown to be abnormal in amount. Except for Wright's observations of leucopenia in conductors we do not know of any demonstrable abnormalities in them, nor can we disclose any difference between the mothers of hemophilic stock who are conductors and those who are not conductors.

Experimental Hemophilia

In 1916[17] while working in Howell's laboratory I demonstrated the anticoagulating action of two phosphatides; one isolated from the heart muscle and the other from the liver. Howell and Holt[18] have shown that the addition of these phosphatides to normal blood in vitro or in vivo produces a diminution in the amount of circulating prothrombin and a relative (in fact often an actual) increase in the amount of antithrombin. The injection of the phosphatides into the circulation (in dogs) caused no constitutional symptoms and resulted in the blood findings characteristic of hemophilia and also the characteristic oozing of blood from wounds made in inserting cannulas, etc., for the experiment. It would be interesting to submit normal platelets to the action of these phosphatides to determine if they would become fixed and unavailable as sources of prothrombin and cephalin.

Diagnosis

From the standpoints of treatment and prognosis the establishment of the diagnosis is of great moment. Although we have Howell's method of testing for a delayed prothrombin time to rely on, the following points should be borne in mind.

1. While it must be remembered that the question of the spontaneous origin of hemophilia is still an open one, pending the examination of the

blood prothrombin time in a sufficient number of cases, the history of bleeding in the ancestors and collaterals of the patient is of prime importance and should be searched for with thoroughness. However, bleeding from certain sites is so common, especially epistaxis, hematemesis and hematuria, that it is comparatively a simple matter to construct a pedigree of bleeders in a family.

2. No single hemorrhage is adequate to establish the presence of the condition unless the characteristic blood changes are found. It is necessary to show that the subject has suffered repeated hemorrhages, if not from birth then from infancy, and that these hemorrhages have occurred from various parts of the body.

3. And further, that injuries such as cuts, skin bruises, sprained joints and loss of teeth, of minor importance to normal persons, give rise in the patient to at least unusual hemorrhage.

4. The male sex only is affected.

Determination of the Coagulation and Prothrombin Times

The test should be made with blood which is free from admixture of tissue juice (cephalin); for Howell[8] has shown that the addition of cephalin to hemophilic blood in vitro markedly reduces the time required for the clot to form. Moreover, in obtaining blood from one of his hemophilic patients on one occasion the needle entered the vein only after several mistrials resulting in considerable laceration of the tissues and the introduction of the tissue juice into the needle and the blood which was finally obtained. Two cubic centimeters of the blood taken by this faulty technique clotted in ten minutes, whereas two cubic centimeters of blood taken from the same patient, just afterwards, using another vein and the correct technique had a coagulation time of between four and five hours. Methods of determining the coagulation time in which the blood is obtained by punctures through the skin are not suitable, for the specimen secured in this manner certainly is admixed with tissue juice.

Coagulation Time Test, Howell's Method

The specimen of blood is obtained from one of the superficial veins of the arm by means of a graduated syringe (Luer form). Six c.c. of blood are taken. Two c.c. are immediately and carefully ejected into a small glass vial or test-tube having a diameter of approximately 21 mm. The test-tube is carefully inclined at intervals in order to observe the state of fluidity. The end point is the moment that the clot is firm enough to permit inversion of the tube. Normal blood tested by this method clots usually in about twenty to forty minutes at room temperature.

Prothrombin Time Test

The remaining 4 c.c. are emptied into a centrifugal tube containing 0.5 c.c. of a 1 per cent. oxalate solution (made up in 0.9 per cent. sodium chloride). After mixing by inverting the tube the specimen is centrifugalized at high speed for twenty minutes to secure a clear plasma, which is pipetted off. Five drops of this plasma are placed in each of four tubes and to these are added in series 2, 3, 4, and 5 drops of a 0.5 per cent. solution of calcium chloride, with the idea of obtaining in one of the tubes the optimum concentration of calcium to cause clotting. The clotting in the tube showing the shortest time of coagulation is compared with the corresponding one of a series similarly prepared from normal blood. According to Howell and others who have used his method, the clotting of normal blood plasma tested by this method is remarkably uniform varying between nine and twelve minutes. The time required for the clot to form in hemophilic blood plasma is greatly prolonged: two to five hours.

Diagnosis from Purpura Hemorrhagica

Hemophilia is sometimes confused with purpura hemorrhagica. However this will not happen if the following points are kept in mind:

Purpura Hemorrhagica	*Hemophilia*
1. Occurs in males and females.	1. Occurs only in males.
2. No hemorrhages in joints.	2. Joint hemorrhages common.
3. Not inherited.	3. Inherited.
4. Normal coagulation time.	4. Delayed coagulation time.
5. Platelets reduced in number.	5. Normal number of platelets.
6. Prolonged bleeding time.	6. Normal bleeding time.
7. Soft, non-retractile clot.	7. Firm, retractile clot.
8. No reclotting phenomenon.	8. Reclotting phenomenon present.
9. Purpuric skin blotches present.	9. Absent.
10. Normal prothrombin time.	10. Delayed prothrombin time.

Chronic purpura hemorrhagica, particularly of the intermittent variety, presents greater diagnostic difficulties but can be differentiated by the decreased platelet count in the chronic purpura hemorrhagica.

Hereditary multiple angiectases or familial epistaxis, causing repeated nose bleeds, need to be recognized and sharply distinguished from hemophilia. There should be no great difficulty in distinguishing these two if the former condition is kept in mind as a possibility and the angiectases are looked for.

In melena neonatorum there occurs a delayed coagulation time perhaps associated with prothrombin deficiency. The condition appears in the first week of life and if the patient recovers it does not recur. Advanced atrophic cirrhosis, phosphorus and chloroform poisoning, conditions in which the liver tissue is damaged, may cause hemorrhages due to a diminution in the amount of circulating fibrinogen, which factor is normal in hemophilic blood. In scurvy the prothrombin time is normal. None of these conditions, however, should be confused with hemophilia.

PROGNOSIS

A better understanding of the defect in hemophilic blood, coupled with more widespread knowledge of and skill in administering serum therapy and blood transfusion, has brightened the prognosis in this condition. Osler states that bleeder children rarely die at birth, however v. Etlinger[19] has gathered statistics which indicate that the first year of life is a most critical period. Childhood, that age in which the youngster is subject to trauma from falls and injuries, the eruption of teeth, or even the normal strain of play is undoubtedly the most dangerous period. However, if adequate medical therapy can be secured to combat the disease in this period, it is encouraging to reflect that as the individual becomes older the blood tends to become more coagulable, and hemorrhages become less frequent on account of this and also because the subject has learned caution from the experiences of his youth. Wickham Legg collected only nine cases which outlived the disease, although there are quite a few recorded cases of hemophilics attaining old age.

Aside from a fatal termination, the most distressing result of this affliction is the deformity which may occur in one or more joints, sometimes going on to ankylosis

TREATMENT

If we grant that de novo cases do not arise it would be possible to completely stamp out the disorder by preventing the marriage of hemophilics and conductors. However, this method is not practical.

Children born of hemophilic stock should not be operated upon until it is determined that they have not inherited the disorder. Even such minor operations as lancing the gums and circumcision are contraindicated although scarification of the skin for vaccination may be performed without danger. It is needless to say that no surgeon should operate before he has ascertained that the patient is not of bleeder stock and before he has satisfied himself that the coagulation time, or better the prothrombin time, is normal. Hemophilic children should be instructed in the danger involved in rough play, from cuts through the skin into the tissues and from falls. They should be granted freedom from corporal punishment. The general health should be maintained at a high level by such upbuilding measures as adequate food, rest and recreation.

Local Measures

1. Compression and ligatures of the arteries and veins leading to or from the source of bleeding are of no avail because the bleeding is invariably a persistent oozing from capillaries, the collateral circulation being sufficient to maintain the bleeding.

2. Styptics of an escharotic nature are useless for the bleeding continues under and around the periphery of the plug of devitalized tissue forming the eschar. The application of the cautery, ferric chloride, calcium salts and gelatin (two to five per cent.) (Sahli), certainly have not produced uniformly satisfactory results in the hands of various workers. One to ten per cent. solutions of cocaine and 1/1,000 adrenalin-chloride have also been used locally. Adrenalin-chloride does constrict the vessels if given locally, but unless the hemorrhage ceases promptly, the bleeding is liable to be more furious when the effect of the drug wears off and the relaxation takes place. Wooldridge conceived the use of "tissue fibrinogens" for the arrest of hemorrhage, and later Wright employed a saline solution of minced thymus gland with success. We now know that the substance in the tissues which physiologically accelerates the clotting of blood is the phosphatide, cephalin[20, 21]. This substance when added to hemophilic blood will cause it to clot promptly and firmly as many workers have shown in vitro. Howell[22], Hurwitz and Lucas[23] and others have secured excellent results from its use and recommend its efficacy in controlling local hemorrhage from hemophilics. The substance is easily and promptly prepared as described below. As far as I am aware writers have not emphasized a point which I brought out in connection with its use either therapeutically or in the laboratory, *viz.*: that cephalin loses its thromboplastic power if exposed to the air. Two or three months after its preparation it is worthless. Cephalin is an unsaturated phosphatide which tends to become saturated either by oxidation or reduction. I have proved[24] that the degree of thromboplastic action exhibited is directly dependent upon the degree of unsaturation. It follows that cephalin should be used only in the strictly freshly isolated state. The thromboplastic power may be preserved by keeping the cephalin in vacuum. Hynson, Westcott and Dunning of Baltimore have prepared, according to my directions, surgical gauze which has been immersed in a concentrated ether solution of cephalin. The ether evaporates promptly, the cephalinized gauze may be sterilized immediately and rolled and placed in sterile glass tubes from which the air is withdrawn, and then sealed. This material remains thromboplastically as active for years (at least three years) as fresh cephalin and is always immediately available for use. Of local styptics tried it was alone effective in controlling the hemorrhage from an ugly cut on the forehead of a

hemophilic boy. I had the privilege of using it on him in the Harriet Lane Home of the Johns Hopkins Hospital.

Preparation of Cephalin

Fresh brains are obtained from the slaughter house, cleaned from membranes and blood, ground to a pulp, spread thinly upon glass plates and dried in a current of warm air or in a vacuum dessicator. When thoroughly dry, powder in a mortar and then extract with ether for three or four hours. Filter off the ether in a closed space and repeat the filtration until the filtrate is clear. Evaporate the filtrate to dryness before an electric fan. Extract the residue thoroughly with acetone (to remove cholesterol and cholesterol esters). Drain off the acetone and extract twice with excess of alcohol (to remove most of the lecithin). Drain off the alcohol, allow to dry and keep in vacuum and in a dark place. The residue is an impure, but nevertheless a most active preparation of cephalin. If necessary it may be sterilized by boiling.

Kocher and Fonio have patented a preparation of this substance which they have placed on the market. They claim that the active principle is obtained from the blood platelets. No precautions to keep it from the air are observed.

Another local measure which has been reported as successful is the application of compresses soaked in fresh serum, and Sayer[25] reports the effective use of whole blood applied locally.

Not knowing the ultimate cause of hemophilia we are not able to direct our therapy towards that objective. However, the recent work of Addis, Fonio, Howell, Minot and Lee in locating the cause of the retardation of the clotting has lighted the way toward rational treatment. While we do not know what causes the deficiency in circulating prothrombin and the fixed condition of the platelets, which makes unavailable their supply of prothrombin and cephalin, nevertheless Minot and Lee[9] have made the observations that normal platelets added to hemophilic plasma initiated prompt clotting, whereas hemophilic platelets added to hemophilic plasma in many times the concentration in which normal platelets were added to hemophilic plasma only caused a much delayed clot, which would naturally suggest the intravenous introduction of normal platelets into the hemophilic suffering hemorrhage. As the normal platelets commence to break up as soon as withdrawn from the circulation and as they are difficult to collect, the adequate manner of delivering these elements to the patient is by means of whole blood transfusion. As all substances added to the blood to prevent its coagulation between the time it is collected from the donor or vendor and its subsequent introduction to the patient tend to fix the platelets, it is preferred even if there was no other reason for so doing, not to add any anti-coagulant now in general use for this purpose. (It is hoped that the phosphatide cuorin[21] will prove to be a true physiological anticoagulant.) After the donor's and patient's blood have been matched, *i. e.*, to determine if they are in the same isoagglutination group, the blood should be collected through a paraffined needle inserted into the vein and immediately injected into the patient's circulation. The experiences with blood transfusion for hemophilic hemorrhage in the Johns Hopkins Hospital have been most satisfactory, not only in those cases first seen where they are in a profound anemic state in which blood transfusion serves to check hemorrhage by supplying available prothrombin and cephalin, replacing lost blood and stimulating the bone marrow, but also in cases of persistent oozing from places where it is difficult to apply local measures such as in the recess of the bone after a tooth has been extracted from it. In both types of cases the experience has been that the hemorrhage ceases immediately. That blood transfusion in sufficient volume may exert a marked and immediate influence on the coagulation time in true hemophilia is shown in a case recorded by Minot and Lee in which after removal of 500 c.c. of blood from the patient 600 c.c. were transfused from a healthy donor. The patient's coagulation time before receiving the transfusion was 150 minutes, immediately after the procedure it was normal, that is to say, 7 minutes. Three days later it lengthened to 60 minutes and in five days it was 100 minutes. Three days being generally considered the life of the platelets in the blood stream Minot and Lee look upon this lengthening of the coagulation time, concurrent with the life of the introduced platelets, as further evidence of their view concerning the abnormal role of platelets in hemophilic blood.

Nolf and Herry[26] introduced the use of Witte's peptone, which if introduced into the circulation in small amounts, according to them is more efficient than serum. They believe its action is due to the stimulation of the production of the elements which they believe are lacking in hemophilia, namely, thrombozym and thromboplastic substance. Tixier and Nobecourt report good results from its use. They employ a solution of Witte's peptone 5 gms., sodium chloride 0.5 gms., and distilled water 100 c.c. This is sterilized and 10 to 20 c.c. are injected subcutaneously. If necessary injections may be given daily until the hemorrhages cease.

Serum treatment in hemophilia was introduced by Weil[27] in 1905, although Bienwald[28] used it locally in 1897. In serum we have thrombin already formed so that the role of the platelets is unnecessary. The serum may be introduced intravenously, subcutaneously, or intramuscularly, the dosage being 10 to 15 c.c. intravenously, and 15 to 40 c.c. in the tissues. The best serum to use is that of fresh human serum not hemolytic to hemophilic blood, although Weil, Leary and Lucas have employed rabbit serum with success and also horse serum freshly drawn and in the form of antidiphtheric serum, one or two injections daily until the hemorrhage is controlled. As serum becomes old the thrombin changes into an inactive state, metathrombin[22]. Weil observed that serum that had been standing even two weeks was not as effective as fresh serum. All commercial serum is six weeks to six months old. Broca [29] claimed success in preventing hemorrhage in four cases by serum injections every three months, bringing coagulation time down from two to three hours to twenty to thirty minutes. Addis reports that the injection of fresh human serum produced a marked diminution in clotting time followed by a reaction in lengthening them back to usual time. Weil did not credit serum treatment with as much success in the therapy of true (hereditary) hemophilia as in bleedings from other causes and Baum seriously questioned its usefulness and efficiency in this field. Defibrinated blood has also been employed with the advantage of supplying erythrocytes to the patient in addition to the plasma.

However, serum treatment has given way to whole blood transfusion which has become relatively a simple procedure. While a few years ago one would certainly administer serum instead of risking the then major operation of direct blood transfusion, now with greatly simplified technique, better understanding of blood groups and absence of any danger to donor or recipient, the latter method has become recognized, in view of the results obtained, as the most rational and effective method of controlling hemorrhage.

Wright claimed to have gotten good results from the administration of calcium salts by mouth, but later workers have not found that calcium salts lessened the tendency to bleed. Its use is probably best limited to bleeding conditions in which an actual deficiency exists. Certainly there is no indication for its use in hemophilia.

Gelatin (five per cent.) (Sahli), administered by mouth or intravenously and subcutaneously, has not given constant benefit. Boggs could not credit it with any power to increase the coagulability of the blood. Sahli also recommended the repeated venepuncture, believing that this procedure stimulated the production of the thromboplastic substance.

Cephalin has been administered internally to hemophilic patients by Howell[22] and by Hurwitz and Lucas[23]. A boy was admitted to the Harriet Lane Home with a history of joint troubles and long continued bleeding from slight injuries. Examination of his blood showed a hemophilic condition, although the family history gave no indication of an hereditary factor. The boy was given 100 c.c. of a solution of cephalin daily for three weeks while in the hospital, and subsequently the same amount daily on alternate weeks over a period of six months. The blood examinations were as follows:

Before treatment { Coagulation time 2 c.c. = 75 to 80 mins.
Prothrombin time = 55 to 60 mins.

After three weeks' daily treatment	Coagulation time	2 c.c.	= 80 mins.
	Prothrombin time		= 43 mins.
After six months' treatment alternate weeks	Coagulation time	2 c.c.	= 50 mins.
	Prothrombin time		= 28 mins.

A second case was treated in a similar way under the direction of Dr. C. R. Drinker. The patient, a young man twenty years of age, entered the Peter Bent Brigham Hospital with a long history of swollen and painful joints and frequent severe and dangerous hemorrhages. He was given cephalin solution by mouth over a period of thirteen weeks. Four examinations of the blood were made:

Before treatment, January 22	Coagulation time	= 47 mins.
	Prothrombin time	= 32 mins.
March 23	Coagulation time	= 50 mins.
	Prothrombin time	= 28 mins.
After seven weeks' treatment	Coagulation time	= 35 mins.
	Prothrombin time	= 28 mins.
After nine weeks' treatment	Coagulation time	= 30 mins.
	Prothrombin time	= 24 mins.
After thirteen weeks' treatment	Coagulation time	= 34 mins.
	Prothrombin time	= 19 mins.

The patient reported a marked improvement in his condition. The treatment is simple and not attended by any untoward symptoms and the results so far obtained, according to Howell, are sufficiently encouraging to warrant a careful trial. Hurwitz and Lucas[23], on the other hand, were not able to attribute to cephalin administered orally any effect in reducing the coagulation time. Cephalin administered intravascularly caused a temporary reduction in the coagulation time followed by a swing in the opposite direction.

Hemophilic joints are best treated by absolute rest in bed until the blood is entirely absorbed. The period may vary from a few days until a month or more. If bone destruction has taken place and limitation of motion has resulted, and if the process is going on to complete ankylosis, then the arm or the leg should be fixed in a serviceable position while there is still some motion so that after ankylosis has set in the member may be of some service to the victim.

To sum up, it would appear that the local lesions in hemophilia may be successfully treated either by the local application of serum or in some cases by styptics. In those cases where local measures are not readily nor efficiently employed, or in severe cases in which profound anemia has intervened, blood transfusion has given the most prompt and constant results.

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